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Norepinephrine ignites local hot spots of neuronal excitation:
How arousal amplifies selectivity in perception and memory

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Short Abstract

Arousal sometimes enhances and sometimes impairs perception and memory. In our Glutamate Amplifies Noradrenergic Effects (GANE) model, glutamate at active synapses interacts with norepinephrine released by the locus coeruleus to create local ‘hot spots’ of activity that enable the selective effects of arousal. This hot spot mechanism allows local cortical regions to self-regulate norepinephrine release based on current activation levels. In turn, hot spots bias global energetic delivery and functional network connectivity to enhance processing of high priority representations and impair processing of lower priority representations.

Long Abstract

Existing brain-based emotion-cognition theories fail to explain arousal’s ability to both enhance and impair cognitive processing. In the Glutamate Amplifies Noradrenergic Effects (GANE) model outlined in this paper, we propose that arousal-induced norepinephrine (NE) released from the locus coeruleus (LC) biases perception and memory in favor of salient, high priority representations at the expense of lower priority representations. This increase in gain under phasic arousal occurs via synaptic self-regulation of NE based on glutamate levels. When the LC is phasically active, elevated levels of glutamate at the site of prioritized representations increase local NE release, creating “NE hot spots.” At these local hot spots, glutamate and NE release are mutually enhancing and amplify activation of prioritized representations. This excitatory effect contrasts with widespread NE suppression of weaker representations via lateral and auto-inhibitory processes. On a broader scale, hot spots increase oscillatory synchronization across neural ensembles transmitting high priority information. Furthermore, key brain structures that detect or pre-determine stimulus priority interact with phasic NE release to preferentially route such information through large-scale functional brain networks. A surge of NE before, during or after encoding enhances synaptic plasticity at sites of high

glutamate activity, triggering local protein synthesis processes that enhance selective memory consolidation. Together, these noradrenergic mechanisms increase perceptual and memory selectivity under arousal. Beyond explaining discrepancies in the emotion-cognition literature, GANE reconciles and extends previous influential theories of LC neuromodulation by highlighting how NE can produce such different outcomes in processing based on priority.

1. Introduction

When jolted by a rough skydiving landing, psychologist James Easterbrook observed that his sense of space and time shrank and slowly re-expanded (Easterbrook, 1982). This sparked his curiosity about how arousal influenced attention. Later he published a review paper that argued that under arousal, people rely more on central or immediately relevant information and less on peripheral information (Easterbrook, 1959). Since his seminal paper, researchers accumulated many more observations that arousal evoked by emotional events enhances some aspects of perception and memory but impairs others (for reviews see Mather & Sutherland, 2011; Reisberg & Heuer, 2004). For instance, victims of a crime tend to remember the weapon vividly but forget the perpetrator's face (Steblay, 1992). People also pay attention to emotional information at the expense of neutral information (Dolcos & McCarthy, 2006; Knight et al., 2007). These examples fit with Easterbrook's formulation that arousal impairs attention to peripheral information. But arousing stimuli can sometimes enhance memory of peripheral neutral information (Kensinger, Garoff-Eaton, & Schacter, 2007; Knight & Mather, 2009). Thus, while it is clear that arousal shapes attention and memory, knowing that something is neutral or spatially peripheral is not enough to predict how it will fare under emotional conditions.

So, then, how does arousal influence the brain's selection of features to highlight versus suppress? An initial answer to this puzzle was provided by the **arousal-biased competition (ABC) model**, which posits that arousal does not have fixed rules about which type of stimuli to enhance or suppress. Instead, arousal amplifies the stakes of on-going selection processes, leading to "winner-take-more" and "loser-take-less" effects in perception and memory (Mather & Sutherland, 2011). ABC builds upon biased competition models proposing that stimuli must compete for limited mental resources (Beck & Kastner, 2009; Desimone & Duncan, 1995; Duncan, 2006). As conceptualized by Desimone and Duncan (1995), both bottom-up and top-down neural mechanisms help resolve competition.

Bottom-up processes are largely automatic, determined by the perceptual properties of a stimulus, and do not depend on top-down attention or task demands. For instance, stimuli that contrast with their surroundings, such as a bright light in a dark room, engage attention automatically even if they are currently goal-irrelevant (Itti & Koch, 2000; Parkhurst, Law, & Niebur, 2002; Reynolds & Desimone, 2003). Top-down goals can also bias competition in favor of particular stimuli that otherwise would not stand out. Although not included in the original biased competition models, past history with particular stimuli is also a source of selection bias (Awh, Belopolsky, & Theeuwes, 2012; Hutchinson & Turk-Browne, 2012). For instance, one's name or a novel stimulus tend to engage attention (Moray, 1959; Reicher, Snyder, & Richards, 1976). In addition, faces, text, and emotionally salient stimuli each grab attention (e.g., Cerf, Frady, & Koch, 2009; Knight et al., 2007; MacKay et al., 2004; Niu, Todd, & Anderson, 2012).

A core aspect of most current theories of visual attention is that these different signals are integrated into maps of the environment that indicate the priority or salience of stimuli across different locations (Itti & Koch, 2000; Soltani & Koch, 2010; Treisman, 1998). Regions in frontoparietal cortex integrating sensory and top-down signals help represent such priority maps (Ptak, 2012). Moreover, having both feedforward and feedback connections between sensory regions and cortical priority maps enables distributed representations of prioritized information to modulate their own processing (e.g., lower-level visual features) even further (Klink, Jentgens, & Lorteije, 2014; Ptak, 2012; Serences & Yantis, 2007; Soltani & Koch, 2010). Thus priority signals are self-biasing to enhance efficient information processing in the brain.

In the ABC model, arousal further biases mental processing to favor high over low priority representations, regardless of whether initial priority is determined by bottom-up salience, emotional salience or top-down goals. Thus, because spatially peripheral information is usually lower priority than central information, arousal usually impairs memory for it (Waring &

Kensinger, 2011 7433; Steblay, 1992). Yet when peripheral information is perceptually salient or goal-relevant, arousal instead enhances memory for it (e.g., Kensinger et al., 2007).

But the ABC model did not tackle how this works in the brain. Previous brain-based models of emotion and cognition also do not account for the dual role of arousal. Most models posit that the amygdala enhances perception and memory consolidation of emotionally salient stimuli, but fail to address how arousal sometimes enhances and sometimes impairs information processing.

In this paper we propose the **Glutamate Amplifies Noradrenergic Effects (GANE) model** in which arousal amplifies the activation difference between high and low neural priority representations via local synaptic self-regulation of the locus coeruleus-norepinephrine (LC-NE) system. According to GANE, hearing an alarming sound or seeing something exciting leads to a surge in NE release, which in turn enhances activity of neurons transmitting high priority mental representations and suppresses activity of neurons transmitting lower priority mental representations. As outlined above, priority is determined by top-down goals, bottom-up factors and high-level stimulus features (Beck & Kastner, 2009; Desimone & Duncan, 1995; Fecteau & Munoz, 2006).

According to GANE, the brain's primary excitatory neurotransmitter, glutamate, signals priority. Under arousal, elevated glutamate associated with highly active neural representations stimulates greater NE release, which then further increases glutamate via positive feedback loops. Thus, in these local "hot spots" glutamate signals are amplified. At the same time, lower thresholds of activation for inhibitory adrenergic autoreceptors suppress activity wherever NE is released and fail to ignite a local hot spot. Higher NE concentration also enhances energetic resource delivery to the site of active cognition, synchronizes brain oscillations, and modulates activity in large-scale functional networks. Thus, under arousal, local NE hot spots contrast with

widespread NE suppression to amplify priority effects in perception and memory, regardless of how priority was instantiated.

2. Arousal-biased competition (ABC) in perception and memory

We start by reviewing recent findings supporting Mather and Sutherland's (2011) ABC model and its novel predictions. Next, we turn to the question of how these arousal effects operate in the brain. A fundamental challenge in understanding how arousal influences cognition is that it sometimes enhances and sometimes impairs information processing. While most emotion research focuses on how processing of emotional stimuli is enhanced compared with neutral stimuli, emotional arousal can also influence processing of neutral stimuli – and across studies, opposing effects are often seen. How can emotionally salient stimuli sometimes enhance memory for what just happened but other times impair it? When will arousing stimuli enhance perception and when will they impair perception of subsequent stimuli? Many studies show that emotion increases selectivity (for reviews see Levine & Edelstein, 2009; Mather & Sutherland, 2011; Murray, Holland, & Kensinger, 2013), but how do we predict what gets selected?

2.1. Arousal enhances perception of salient stimuli, but impairs perception of inconspicuous stimuli.

In previous research on how arousal influences subsequent perception, there were two types of findings that were hard to reconcile. First, arousing stimuli impair perceiving subsequent stimuli. For instance, people preferentially perceive arousing stimuli (e.g., Anderson, 2005; Keil & Ihssen, 2004) but fail to perceive or encode neutral stimuli nearby either in time (e.g., embedded in a rapid series of images after an arousing image; Smith, Most, Newsome, & Zald, 2006) or in space (Kensinger et al., 2007; Tooley, Brigham, Maass, & Bothwell, 1987). But in the second type of finding, hearing or seeing an arousing stimulus enhances visual perception of a subsequent Gabor patch (Padmala & Pessoa, 2008; Phelps, Ling, & Carrasco, 2006).

How can we explain both the enhancing and impairing effects of arousing stimuli on perception of stimuli that appear nearby in time or space? Initial evidence supports the ABC hypothesis that inducing arousal should have opposite effects on perception: arousal should enhance processing of high priority (more salient) but impair processing of lower priority (less salient) stimuli. When asked to report as many letters as they could from a briefly flashed array (see Fig. 1), participants reported more of the high salience letters and fewer of the low salience letters if they had just heard an arousing emotionally negative sound than if they had just heard a neutral sound (Sutherland & Mather, 2012). Similar results were seen when arousal was induced by emotionally positive sounds (Sutherland & Mather, under review). These results indicate that arousal makes salient stimuli stand out even more than they would otherwise.

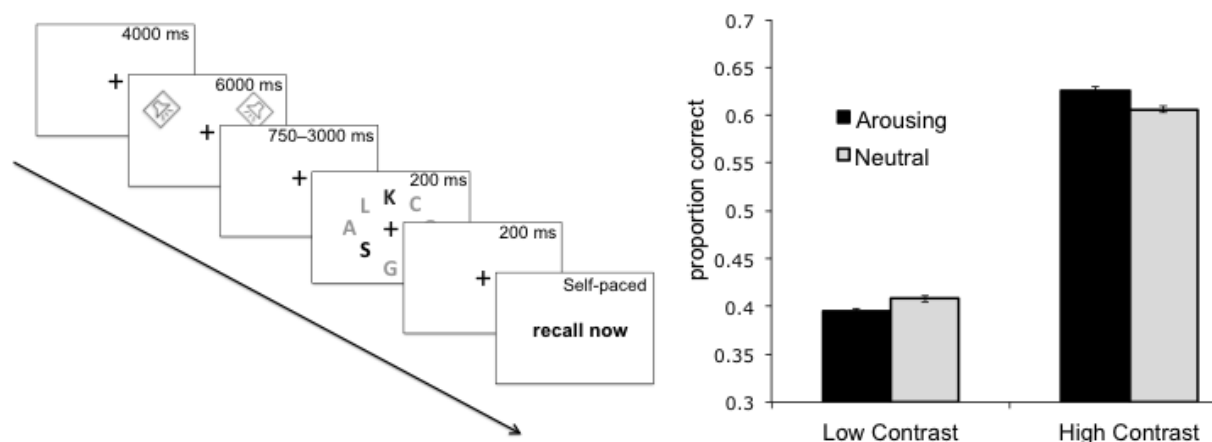


Figure 1. Participants heard an arousing or neutral sound before a letter array was flashed briefly. They then reported as many of the letters as they could. Some of the letters were shown in dark grey (high contrast and therefore salient) and some in light grey (low contrast and less salient). Participants reported a higher proportion of the salient letters than the non-salient letters, but this advantage for salient letters was significantly greater on arousing trials than on neutral trials, and the disadvantage for the non-salient letters was significantly greater on arousing than on neutral trials (Sutherland & Mather, 2012).

ABC also explains the enhanced processing of emotional stimuli, the focus of most previous theoretical accounts (e.g., Kensinger, 2004; LaBar & Cabeza, 2006; Mather, 2007; Murty, Ritchey, Adcock, & LaBar, 2010; Phelps, 2004). People tend to prioritize emotional stimuli due to top-down goals (e.g., increasing pleasure and avoiding pain), their emotional saliency (e.g., associations with reward/punishment) and/or bottom-up salience (e.g., a gunshot is loud as well as a threat to safety; Markovic, Anderson, & Todd, 2014). Thus, arousing stimuli should dominate competition for representation at their particular spatiotemporal position (Wang, Kennedy, & Most, 2012).

If the arousing stimulus appears in the exact same location as a neutral stimulus presented less than a second later, it will impair perception of that neutral stimulus, an effect known as emotion-induced blindness (Kennedy & Most, 2012; Most, Chun, Widders, & Zald, 2005). On the other hand, arousing stimuli tend to enhance the dominance of high priority stimuli that are nearby but not competing for the same spatiotemporal spot. An emotionally salient word that impairs perceiving a subsequent target word flashed in the same location 50 or 500 ms later can instead enhance perceiving a target word flashed 1000 ms later (Bocanegra & Zeelenberg, 2009), because after the longer interval, the priority of the target word is no longer overshadowed by the emotionally salient word.

2.2. Arousal enhances perceptual learning about salient stimuli but impairs learning about non-salient stimuli.

In visual search, target salience depends on target-distractor similarity. Interspersing emotional or neutral pictures with a visual search task, had opposite effects on perceptual learning about salient and non-salient targets (Lee, Itti, & Mather, 2012). Emotional images enhanced perceptual learning of the exact tilt of a salient target line appearing in an array of distracting

lines but impaired learning about a non-salient target (Fig. 2). Thus, whether arousal enhanced or impaired learning depended on the target's salience.

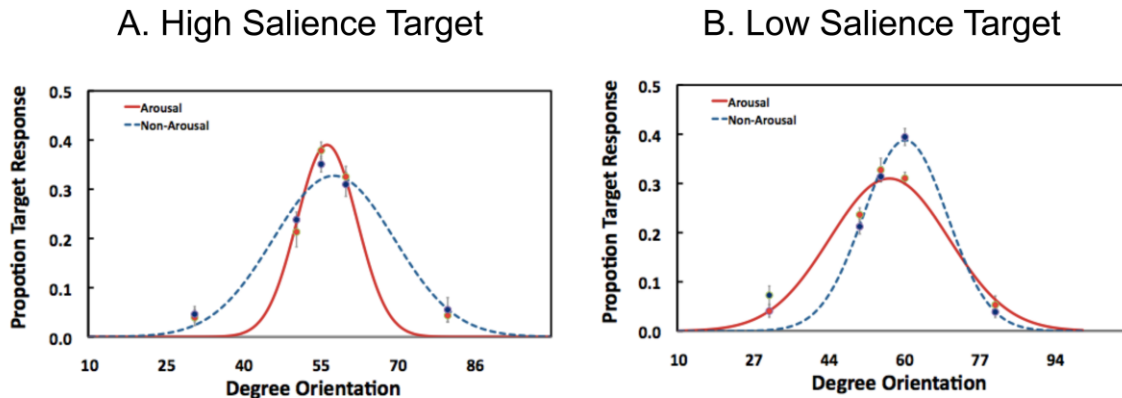


Figure 2. Estimated tuning curves for averaged “target” responses as a function of emotion in the high-salience condition (A) and low-salience condition (B). In the high salience condition, having interspersed emotional pictures enhanced perceptual learning of the exact tilt of the target (55°), whereas in the low salience condition, emotion impaired learning the exact tilt of the target. Figure adapted from Lee et al., (2012).

2.3. How arousal modulates neural representations depends on salience.

A recent study took advantage of the fact that faces and scenes activate distinct representational regions in the brain to test the ABC hypothesis that arousal increases brain activation associated with processing salient stimuli while decreasing brain activation associated with processing less salient stimuli (Lee, Sakaki, Cheng, Velasco, & Mather, 2014). On each trial, one yellow-framed face and one scene image appeared briefly side-by-side, followed by the appearance of a dot behind one of the images (Fig. 3A). The participants' task was to indicate which side the dot was on. Participants responded fastest to dots that appeared behind the salient faces on trials preceded by a tone conditioned to predict shock and thereby induce arousal. In a follow-up fMRI study, there was an arousal-by-saliency interaction in visual

category-specific brain regions, such that arousal enhanced brain activation in the region processing the salient stimulus (i.e., fusiform face area) but suppressed brain activation in the region processing the non-salient stimulus (i.e., parahippocampal place area, see Fig. 3B; Lee et al., 2014).

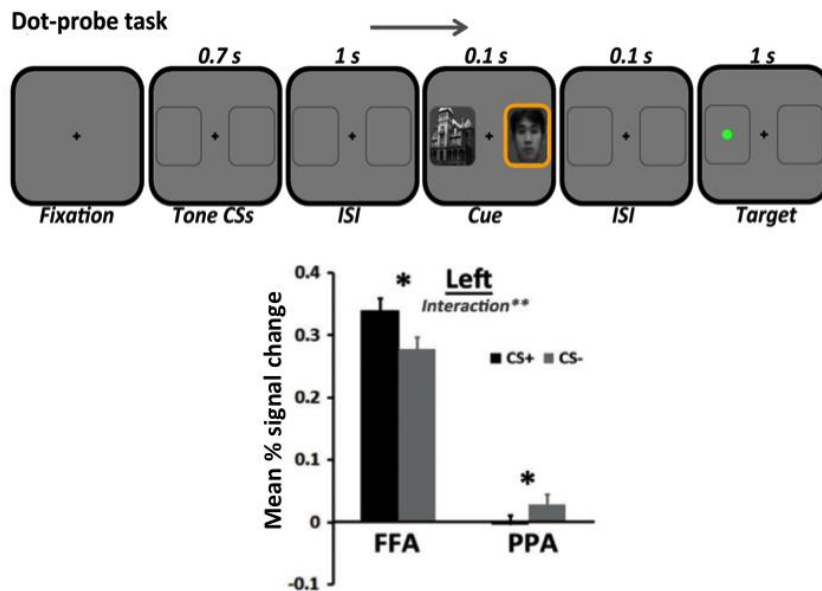


Figure 3. In Lee et al.'s (2014) fMRI study, tones conditioned to predict shock (CS+ tones) played before the display of a salient face and a less salient scene increased activity in the left fusiform face area (FFA) associated with face processing, while decreasing activity in the left parahippocampal place area (PPA) associated with the scene processing, compared with tones conditioned not to predict shock (CS- tones). * $p < .05$, ** $p < .005$.

2.4. Arousal enhances or impairs memory consolidation of representations depending on their priority.

So far, we have focused on how arousal enhances processing of subsequent inputs. However, arousal should have similar effects on mental representations currently active at the moment arousal is induced. Previous research indicates that arousal induced after initial encoding

sometimes impairs and sometimes enhances memory of preceding information (Knight & Mather, 2009). The critical ABC hypothesis is that experimentally manipulating priority of information should alter the effect of subsequent arousal on memory consolidation.

In the first study testing this hypothesis, participants viewed lists of objects one object at a time, with one perceptual oddball in each list (Fig. 4; Sakaki, Fryer, & Mather, 2014). The oddball was either emotionally salient or neutral. Some participants were asked to recall the name of the oddball picture as soon as the list presentation ended. In this condition, the object shown just before the oddball (e.g., the cabbage in Fig. 4) was low priority. Other participants were asked to recall the name of the object shown just before the oddball (oddball-1 object). Thus, in this condition, the oddball-1 object (e.g., the cabbage) was high priority. After a series of lists, memory for the details of all the oddball-1 objects was tested. As predicted, when the oddball pictures had been positively or negatively emotionally salient, memory for prioritized oddball-1 objects was enhanced whereas memory for non-prioritized oddball-1 objects was impaired.

While the brain mechanisms underlying this priority by arousal interaction in *memory* have yet to be tested, there is fMRI evidence that arousal enhances activity in regions processing a high priority stimulus. For instance, pairing shock with certain high priority (i.e., standalone) neutral scenes enhances successful encoding-related activity in the PPA, the brain region specialized to process scene information (Schwarze, Bingel, & Sommer, 2012). Thus, arousal-induced enhancement of brain activity processing prioritized information not only occurs during perception (e.g., Lee et al., 2014) but also predicts memory for such items.

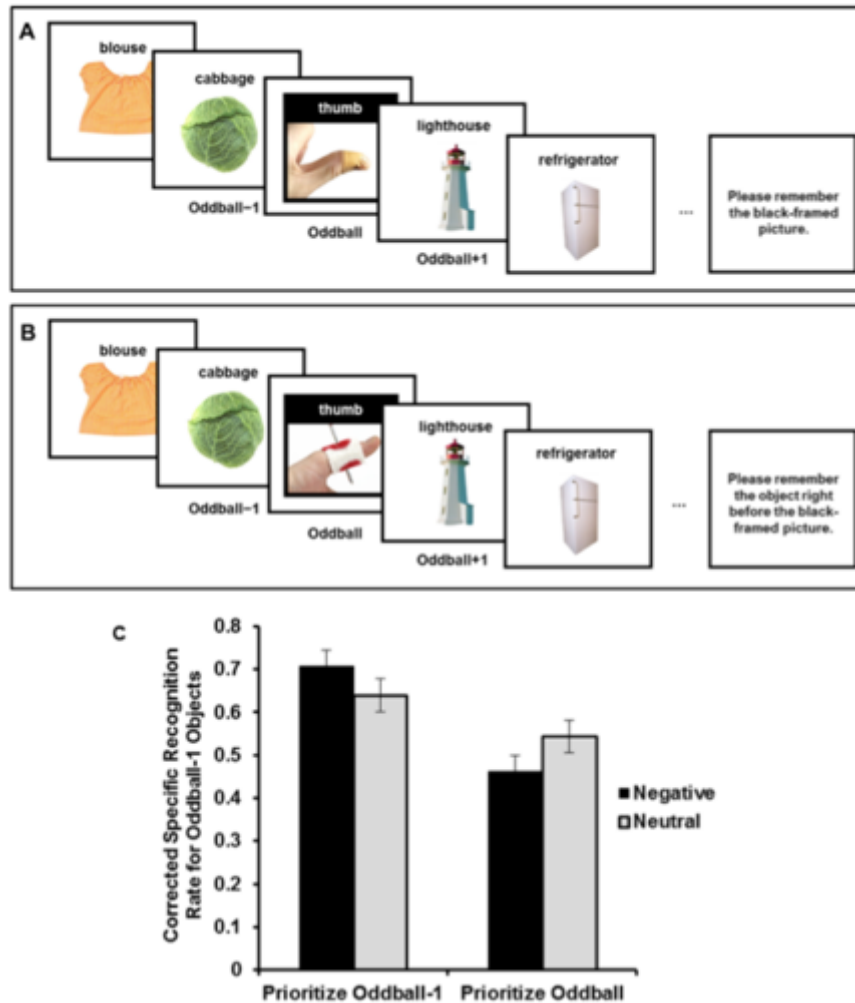


Figure 4. Schematic representations of a neutral trial in the prioritize-oddball condition (A) and a negative trial in the prioritize-oddball-1 condition (B). Memory performance for oddball-1 objects differed as a function of their priority and the valence of oddball pictures (C). Oddball pictures depicted here were obtained from iStockPhoto for illustration purposes and differ from those used in the experiments. Figures from Sakaki et al. (2014).

2.5. Summary.

Mather and Sutherland's (2011) ABC model accounts for both the enhancement and impairment effects of arousal on neutral stimuli across a wide variety of experimental contexts. It makes novel predictions: 1) Arousal before exposure to stimuli should amplify the effects of salience on

perception and memory encoding; 2) Arousal shortly after encoding information should amplify the effects of its goal relevance on memory consolidation. Both effects are due to arousal modulating representations based on priority. Other models also highlight the importance of interactions between arousal, attention and goals (Kaplan, Van Damme, & Levine, 2012; Levine & Edelstein, 2009; Montagrin, Brosch, & Sander, 2013; Talmi, 2013). However, so far there has been no account of how arousal amplifies the effects of priority in the brain.

3. Current brain-based models of arousal's modulatory effects.

Before we present our account of how arousal can modulate neural representations differently depending on their priority, we outline how existing brain-based models of arousal and cognition fail to adequately address how arousal has opposite effects depending on representational priority (see Table 1 for an overview).

3.1. Modular vs. "multiple waves" of emotion enhancement in perception.

Noticing things like snakes and guns can increase the odds of survival. Consistent with this adaptive importance, studies show that emotionally salient stimuli are often detected more rapidly than neutral stimuli (Leclerc & Kensinger, 2008; Mather & Knight, 2006; Öhman, Flykt, & Esteves, 2001). Explaining the privileged status of emotional stimuli has been the focus of brain models of emotion perception. One common assumption is that the evolutionary value of noticing emotional stimuli led to a specialized emotion module or pathway to evaluate emotional salience (Tamietto & de Gelder, 2010). For instance, in their **Multiple Attention Gain Control (MAGiC) model**, Pourtois et al. (2013) argue that emotional salience shapes perception via amplification mechanisms independent of other attentional processes. In the MAGiC model, the amygdala and other modulatory brain regions amplify neural responses to emotional relative to neutral stimuli along sensory pathways. The model also posits that these modulations occur in

parallel to and sometimes compete with signals from bottom-up (exogenous) and top-down (endogenous) attentional control systems (see also Vuilleumier, 2005).

In contrast, Pessoa and Adolphs (2010) argue against a modular approach to emotion enhancement in perception. In their **multiple waves model**, affectively and motivationally significant visual stimuli rapidly engage multiple brain sites, including the amygdala, orbitofrontal cortex, anterior insula and anterior cingulate cortex, that then bias processing to favor these stimuli. From their perspective, the amygdala helps prioritize emotional aspects of information processing by coordinating activity in other regions involved in selective attention. Thus, in the multiple waves model, emotion influences general-purpose perceptual and attention systems rather than harnessing independent brain mechanisms to enhance perception of emotional items.

This latter perspective is more compatible than separate-system models with our findings; if emotional stimuli were processed via a separate system than neutral stimuli, it is not clear how emotional arousal could have both enhancing and impairing effects on neutral stimuli depending on their priority. However, even this modulatory multiple waves approach to emotion-cognition interactions fails to explain the full picture of how emotional arousal influences cognitive processing, as it focuses only on the enhanced perception of arousing stimuli, and ignores how arousal affects perceptual selectivity more generally.

3.2. The canonical amygdala modulation model of emotional memory enhancement.

Noticing something creates initial trace representations that require additional resources over the next few minutes, hours and days to consolidate into a longer-lasting memory. Much research indicates that emotional arousal experienced before, during or after an event can enhance these memory consolidation processes (Hermans et al., 2014). The prevailing view of

how emotion affects memory consolidation is that the amygdala enhances processes in the hippocampus and other memory-related brain regions in the medial temporal lobes, such that memory for emotional events is enhanced compared with memory for neutral events (e.g., McGaugh, 2004). Consistent with this idea, activity in the amygdala during encoding predicts later memory for emotional items but not memory for neutral items, as does greater amygdala functional connectivity with medial temporal brain regions (Dolcos, LaBar, & Cabeza, 2004; Kilpatrick & Cahill, 2003; Richardson, Strange, & Dolan, 2004; Ritchey, Dolcos, & Cabeza, 2008).

Converging rodent and human research indicate that NE facilitates the amygdala-mediated enhancement of emotional information. For instance, NE released in the amygdala during arousal is associated with enhanced memory for the emotionally arousing event (McIntyre, Hatfield, & McGaugh, 2002). Infusing noradrenergic agonists into the basolateral amygdala after training also enhances memory for emotionally arousing events (Hatfield & McGaugh, 1999; LaLumiere, Buen, & McGaugh, 2003). In humans, administration of the β -adrenergic antagonist propranolol impairs emotional memories while pharmacological manipulations that increase NE levels, such as a selective NE reuptake inhibitor, tend to enhance them (Chamberlain & Robbins, 2013), and enhanced amygdala activity during encoding emotional stimuli is reduced by propranolol (Strange & Dolan, 2004). Thus, NE-amygdala interactions enhance memory for emotional events.

NE activation of the amygdala can also impair memory for neutral information that is encountered near something emotional. For instance, as already described above in the context of the Sakaki et al. (2014) study, people often show worse memory for neutral low priority information shown right before an emotional compared with a neutral “oddball” stimulus. Patients with amygdala damage do not show decrements in memory for neutral words

preceding emotional oddball words, and in normal individuals, a β -adrenergic antagonist prevents this retrograde memory impairment (Strange, Hurlemann, & Dolan, 2003).

Although not usually articulated, the amygdala-modulation hypothesis presumably explains these impairment effects for neutral stimuli in terms of a trade-off effect in which the amygdala focuses resources on to emotional stimuli, leaving less available to process and consolidate the neutral stimuli. However, this trade-off explanation fails to explain how NE-amygdala interactions also can enhance memory for non-arousing information (e.g., Barsegyan, McGaugh, & Roozendaal, 2014; Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008).

3.3. Biased attention via norepinephrine model

In the **Biased Attention via Norepinephrine (BANE) model**, Markovic et al. (2014) propose that affectively salient stimuli activate the LC-NE system in order to optimize their own processing. Like ABC (Mather & Sutherland, 2011), BANE builds on biased competition models of attention (Markovic et al., 2014). BANE proposes that affect-biased attention “is distinct from both ‘classic’ executive top-down and bottom-up visual attention, and is at least in part circumscribed by a different set of neural mechanisms” (Markovic et al., 2014, p. 230). In BANE, emotional salience is detected by an ‘anterior affective system,’ including the amygdala and the orbitofrontal cortex, based on the recent history of reward and punishment. In turn, the amygdala’s recruitment of the LC-NE system serves as an additional specialized pathway that further biases attention and memory in favor of the affectively relevant information that triggered NE release.

However, like other models of emotion and cognition, BANE focuses exclusively on how affectively salient stimuli outcompete less salient stimuli, and does not address how arousal

induced by these stimuli sometimes enhances and sometimes impairs processing of proximal neutral information.

3.4. Emotional attention competes with executive attention for limited mental resources.

Another line of work focuses on how emotional stimuli compete for executive resources (Bishop, 2007; Choi, Padmala, & Pessoa, 2012; Eysenck, Derakshan, Santos, & Calvo), with some researchers positing that a ventral affective system competes with a dorsal executive system (Bush, Luu, & Posner, 2000; Dolcos, Iordan, & Dolcos, 2011). For instance, when task-irrelevant emotional stimuli capture attention, they diminish dorsal executive brain region function and therefore disrupt working memory for neutral faces that were just seen (Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Dolcos & McCarthy, 2006). However, meta-analyses indicate that emotional responses are associated with both ventral and dorsal prefrontal cortical regions (Phan, Wager, Taylor, & Liberzon, 2002; Shackman et al., 2011), and so the notion that emotional distractors lead ventral PFC to inhibit dorsolateral PFC (Dolcos et al., 2008) is unlikely to be universal across different contexts.

Instead of a ventral/dorsal antagonism model, the **dual competition model** posits that emotional stimuli compete for resources at both perceptual and executive levels of processing (Pessoa, 2009; Pessoa, 2013). For instance, when participants heard tones predicting shock, regions within the fronto-parietal network activated (Lim, Padmala, & Pessoa, 2009).

Recruitment of these regions during intense emotional arousal should make them less available for concurrent neutral task-related processing and lead to behavioral impairments. At the perceptual level of the dual competition model, both cortical and subcortical structures help amplify visual cortex responses to emotional stimuli, again leading to the impaired perception of other concurrent stimuli.

As in the ABC framework, competition is a core feature of these models. However, these models only consider one type of competition: that between arousing and neutral stimuli/tasks. Critically, our empirical results indicate that arousal also influences competition between two neutral stimuli as well, such that processing high priority stimuli is enhanced, while processing lower priority stimuli is impaired. It is not clear how, in competition models that focus on competition between arousing and neutral stimuli, arousal would interact differently with low and high priority neutral information. For instance, such models cannot account for the differential effects of arousing sounds on subsequent perceptually salient versus non-salient letters (Fig. 1).

3.5. Competition between items for memory consolidation.

In a different type of competition account, Diamond (2005) proposes that there is “ruthless competition” between novel and existing memory representations, such that encoding a new emotional experience suppresses recently potentiated synapses, creating memory for emotional events at the cost of memory for information learned just before the emotional event (Diamond, Park, Campbell, & Woodson, 2005).

This **ruthless-competition hypothesis** argues that the acquisition of new information via the hippocampus depotentiates the most recently activated synapses, and that this suppression of recently formed memories is greater when the new information induces emotion or stress. Thus, inducing arousal should impair memory for a preceding sequence of items, regardless of whether those preceding items were themselves emotional or not. That is not the case, however. Inducing arousal via emotional or cold-pressor stress immediately after participants study a mixed list of emotional and neutral pictures selectively enhances memory for preceding *emotional* but not neutral pictures (Cahill, Gorski, & Le, 2003; Liu, Graham, & Zorawski, 2008).

3.6. An arousing stimulus sometimes impairs and sometimes enhances memory of what just happened beforehand.

How can inducing arousal enhance memory for preceding emotional items but not neutral items? Investigators proposed that emotional arousal “tags” synapses associated with representations of emotional items, making these synapses the selective target of protein-synthesis-dependent long-term potentiation (LTP; Bergado, Lucas, & Richter-Levin, 2011; Richter-Levin & Akirav, 2003; Segal & Cahill, 2009; Tully & Bolshakov, 2010). The **emotional-tagging hypothesis** predicts that emotionally salient stimuli are remembered better than neutral stimuli, because emotional tags allow those particular synapses to capture the plasticity-related proteins released with subsequent inductions of arousal.

A problem for the emotion-tagging model is that inducing emotional arousal sometimes enhances memory for preceding neutral stimuli (Anderson, Wais, & Gabrieli, 2006; Dunsmoor, Murty, Davachi, & Phelps, 2015; Knight & Mather, 2009; Nielson & Powless, 2007; Sakaki et al., 2014). Neither the emotional-tagging nor any of the other hypotheses outlined above can account for this retrograde enhancement of something neutral. In contrast to the emotional-tagging hypothesis, behavioral studies demonstrate that whether something arousing will yield retrograde enhancement or impairment depends on the priority of the preceding information (Section 2.5; Ponzio & Mather, 2014; Sakaki et al., 2014).

3.7. Summary.

While there are many models of how emotion enhances perception, attention, and memory in the brain, these theories fail to account for both the enhancing and impairing effects of emotional arousal (see Table 1 for a summary). In the following sections, we make the case for GANE, a model of how NE released under arousal can impact high and low priority representations differently despite its diffuse release across the brain.

4. Locus coeruleus, NE and arousal

Like GANE, other theories also argue that the LC-NE system is important for emotion-cognition interactions (McGaugh, 2000, 2004; McIntyre, McGaugh, & Williams, 2012; Markovic et al., 2014). However, they have focused mostly on how NE interacts with the amygdala to enhance processing and consolidation of emotional stimuli at the expense of processing neutral stimuli (e.g., Strange et al., 2003; Strange & Dolan, 2004). In contrast, we argue that the LC-NE system promotes selectivity for any prioritized stimuli, irrespective of whether they are emotional or non-emotional.

In this section, we review the functional anatomy of the LC-NE system. A small nucleus in the brainstem known as the locus coeruleus (LC) releases NE when people are aroused - whether it is by a reward or punishment, a loud noise, or a disturbing image. LC axons are distributed throughout most of the brain (Gaspar, Berger, Febvret, Vigny, & Henry, 1989; Javoy-Agid et al., 1989; Levitt, Rakic, & Goldman-Rakic, 1984; Swanson & Hartman, 1975), enabling NE to modify neural processing both locally and more globally in large-scale functional brain networks. How does the LC influence information processing in most cortical and subcortical regions? One might think that a hormone released under conditions of arousal would amp up brain activity. But instead, NE quiets *most* neuronal activity. In turn, this quiet backdrop makes those select few representations that NE amplifies stand out even more.

4.1. Functional neuroanatomy of the LC-NE system.

The LC is the primary source of cortical NE and helps determine arousal levels (Berridge, Schmeichel, & Espana, 2012; Berridge & Waterhouse, 2003; Samuels & Szabadi, 2008a, 2008b). Tonic, or background, levels of LC activity help regulate levels of wakefulness (Carter et al., 2010). Phasic, or transient, bursts of LC activity occur in response to novel, stressful or salient stimuli (Aston-Jones & Bloom, 1981; Foote, Aston-Jones, & Bloom, 1980; Grant, Aston-

Jones, & Redmond Jr, 1988; Sara & Bouret, 2012; Sara & Segal, 1991; Vankov, Hervé-Minvielle, & Sara, 1995) or to top-down signals associated with decision outcomes or goal relevance (Aston-Jones & Cohen, 2005; Aston-Jones, Rajkowski, & Cohen, 1999). Emotionally salient stimuli also induce LC phasic activity irrespective of whether stimuli are positive (Bouret & Richmond, 2015; Grant et al., 1988) or aversive (Chen & Sara, 2007; Grant et al., 1988).

With highly divergent branching axons, the LC projects to every major region of cortex, despite its relatively small number of neurons (13,000 per hemisphere in humans; Foote & Morrison, 1987). Subcortical regions that underlie memory, attention, and emotional processing, including the hippocampus, fronto-parietal cortex and amygdala, are also innervated by the LC (Berridge & Waterhouse, 2003). LC axon varicosities release NE into extracellular space, allowing it to activate a broad swath of receptors within a diffusion zone (Beaudet & Descarries, 1978; Descarries, Watkins, & Lapierre, 1977; O'Donnell, Zeppenfeld, McConnell, Pena, & Nedergaard, 2012).

In target brain sites, NE binds to multiple receptor subtypes (i.e., $\alpha 1$, $\alpha 2$ and β receptors) that are located both pre- and post-synaptically on neurons and astrocytes (O'Donnell et al., 2012; Berridge & Waterhouse, 2003; Terakado, 2014; Tully & Bolshakov, 2010). Whereas $\alpha 2$ -adrenoreceptors limit global and local NE release via autoreceptors and decrease cell excitability, β -adrenoreceptor activation generally increases cell excitability, network activity and synaptic plasticity (Berridge & Waterhouse, 2003; Marzo, Bai, & Otani, 2009; Nomura et al., 2014; Starke, 2001). $\alpha 1$ -adrenoreceptors recruit phospholipase activation and typically increase cell excitability via the inhibition of potassium channels (Wang & McCormick, 1993). Thus, the relative density and localization of adrenoreceptor subtypes helps determine how arousal-induced NE release will affect neural processing in different brain regions.

4.2. NE decreases neuronal noise in sensory regions during arousal.

In the 1970's, researchers proposed that LC-NE activity enhances signal-to-noise ratios in target neurons in sensory regions (Foote, Freedman, & Oliver, 1975; Freedman, Hoffer, Woodward, & Puro, 1977; Segal & Bloom, 1976; Waterhouse & Woodward, 1980). For instance, recording from individual neurons in awake squirrel monkeys revealed that NE application reduced spontaneous activity more than it reduced activity evoked by species-specific vocalizations (Foote et al., 1975).

Noradrenergic regulation of signal-to-noise ratios is characterized by two simultaneous effects: 1) most neurons in a population decrease spontaneous firing, and 2) the few neurons that typically respond strongly to the specific current sensory stimuli either show no decrease or an increase in firing, unlike the majority of neurons for which the stimuli typically evoke weak responses (Foote et al., 1975; Freedman et al., 1977; Hasselmo, Linster, Patil, Ma, & Cekic, 1997; Kuo & Trussell, 2011; Livingstone & Hubel, 1981; O'Donnell et al., 2012; Oades, 1985; Waterhouse & Woodward, 1980).

Intracellular recording data in awake animals support and extend these early observations. Both inhibitory and excitatory neurons are depolarized in aroused cortex when mice run (Polack, Friedman, & Golshani, 2013). Yet, consistent with earlier reports of a quieter cortex under arousal, inhibitory neurons are more depolarized than excitatory neurons (Polack et al., 2013). Moreover, surround inhibition dominates sensory responses during wakefulness compared with anesthesia, increasing the speed and selectivity of responses to stimuli in the center of the receptive field (Haider, Häusser, & Carandini, 2013). NE mediates the increase in widespread depolarization and the increase in inhibitory activity in visual cortex that together increase the signal-to-noise ratio (Polack et al., 2013). The effect of NE has also been characterized as

increasing the gain on the activation function of neural networks (Fig. 5; Aston-Jones & Cohen, 2005).

Arousal is also characterized by cortical desynchronization, both globally when comparing wakefulness to anesthesia (Constantinople & Bruno, 2011) or locomotion to being stationary (Polack et al., 2013) and locally among neurons corresponding to attended representations (Fries, Reynolds, Rorie, & Desimone, 2001). Such decreases in cortical slow-wave synchrony under arousal are likely mediated by LC activity (Berridge & Foote, 1991; Berridge, Page, Valentino, & Foote, 1993). Synchronous slow-wave neural activity may gate sensory inputs, whereas desynchronized activity permits communication of cortical representations of stimuli across the brain (Luczak, Bartho, & Harris, 2013). Cortical cell depolarization, desynchronization, and increased responsiveness to external input also occur with pupil dilation (Reimer et al., 2014; Vinck, Batista-Brito, Knoblich, & Cardin, 2014), and pupil dilation tracks LC activity (Murphy, O'Connell, O'Sullivan, Robertson, & Balsters, 2014).

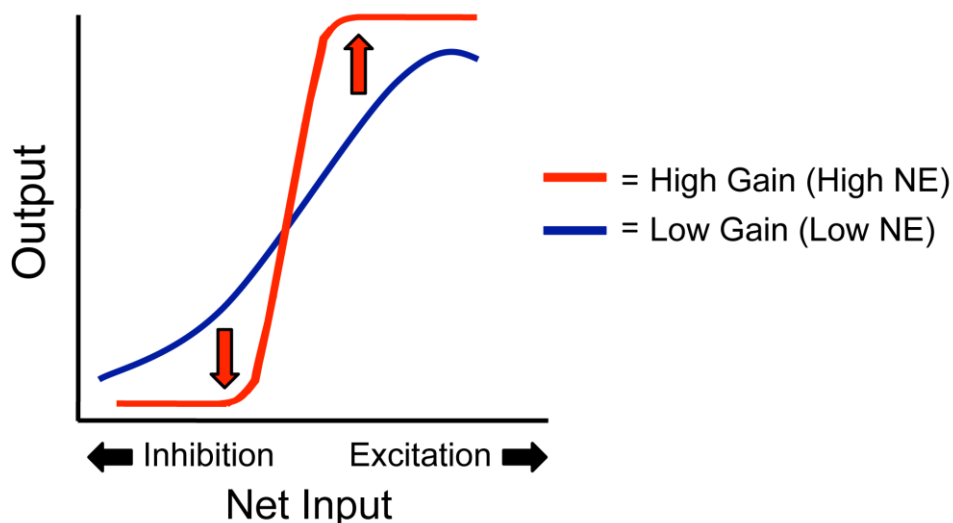


Figure 5. NE gain modulation makes the nonlinear input-output function more extreme, increasing the activity of units receiving excitatory input and decreasing the activity of units receiving inhibitory input. Adapted from Aston-Jones and Cohen (2005).

4.3 Summary.

Years of research indicate that NE suppresses weak or random neuronal activity but not strong activity. This is consistent with the increased selectivity seen under arousal (Section 2). In the next section, we outline a model of how NE has such different outcomes depending on activity level.

5. Glutamate Amplifies Noradrenergic Effects (GANE): the core noradrenergic selectivity mechanism under arousal.

Now we turn to our GANE model, a novel brain-based account of how arousal amplifies priority effects in perception and memory. We propose that local glutamate-NE interactions increase gain under arousal. Glutamate is the most prevalent excitatory neurotransmitter in the brain (Meldrum, 2000). Glutamate receptors such as AMPA and NMDA receptors mediate rapid excitatory synaptic transmission, neural network connectivity and long-term memory (Bliss & Collingridge, 1993; Lynch, 2004; Traynelis et al., 2010).

In addition to point-to-point transmission across a synapse, some glutamate escapes the synaptic cleft, leading to 'glutamate spillover' (Okubo et al., 2010). In this section we outline evidence that glutamate spillover attracts and amplifies local NE release via positive feedback loops. These self-regulating NE hot spots generate even greater excitatory activity in the vicinity of synapses transmitting high priority representations, in contrast with NE's suppressive effects in the more widespread non-hot-spot regions.

The Norepinephrine “Hot Spot” Mechanism

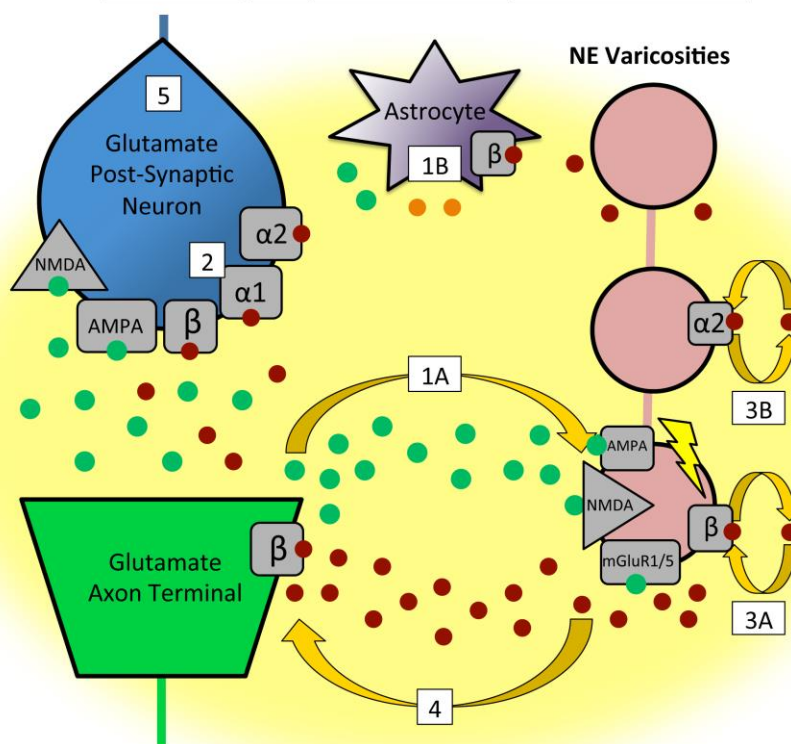


Figure 6. The norepinephrine (NE) “hot spot” mechanism. (1A) Spillover glutamate (green dots) from highly active neurons interacts with nearby depolarized NE varicosities in a positive feedback loop involving NMDA and other glutamate receptors that leads to greater local NE release (maroon dots). The glutamatergic NMDA receptors require concomitant depolarization of noradrenergic axons (lightning symbol). Thus, hot spots amplify prioritized inputs most effectively under phasic arousal. (1B) Glutamate also recruits nearby astrocytes to release serine, glycine (orange dots), and additional glutamate. (2) Greater NE release creates concentration levels sufficient to activate low-affinity β -adrenoreceptors, which enhances neuron excitability. (3) Via activation of β and $\alpha 2$ auto-receptors, NE can stimulate or inhibit additional NE release, respectively. (4) Within hot spots, NE engages β -adrenoceptors on pre-synaptic glutamate terminals to increase glutamate release. (5) Finally, NE binding to post-synaptic β -

adrenoceptors also inhibits the slow afterhypolarization, enabling the neuron to fire for even longer.

5.1. The NE hot spot: How local NE-glutamate positive feedback loops amplify processing of high priority information.

1) High glutamate activity stimulates adjacent NE varicosities to release more NE. The first demonstrations of glutamate-evoked effects on NE found that, via NMDA and non-NMDA glutamate receptors on LC axons, glutamate increased NE release (Fink, Göthert, Molderings, & Schlicker, 1989; Göthert & Fink, 1991; Jones, Snell, & Johnson, 1987; Lalies, Middlemiss, & Ransom, 1988; Nelson, Zaczek, & Coyle, 1980; Pittaluga & Raiteri, 1990, 1992; Vezzani, Wu, & Samanin, 1987; Wang, Andrews, & Thukral, 1992). In these studies, glutamate-evoked NE release occurred for NE varicosities in all cortical structures investigated *in vitro*: olfactory bulb, hippocampus and throughout neocortex. *In vivo* experiments replicated the effect with targeted glutamate in rodent prefrontal cortex (Lehmann, Valentino, & Robine, 1992). Other neurotransmitters associated with arousal, such as histamine (Burban et al., 2010) and orexin (Tose and Hirota 2005), enhance glutamate-evoked NE release. Central to our hypothesis, glutamate-evoked NE release occurs in human neocortex (Fink, Schultheiß, & Göthert, 1992; Luccini et al., 2007; Pittaluga et al., 1999).

How do these glutamate-NE interactions occur? LC axon varicosities rarely make direct synaptic contacts (e.g., only ~5% in rat cortex; Vizi, Fekete, Karoly, & Mike, 2010), but the distribution of these varicosities suggests they should often be found near glutamate terminals at excitatory synapses in neocortex (Benavides-Piccione, Arellano, & DeFelipe, 2005; Gaspar et al., 1989). Another critical piece is that LC neurons produce the NMDA receptor subunits needed for glutamate to modulate the release of NE from LC axon varicosities (Chandler, Gao,

& Waterhouse, 2014; Grilli et al., 2009; Petralia, Yokotani, & Wenthold, 1994; Zhu, Brodsky, Gorman, & Inturrisi, 2003).

New technologies enable the visualization of glutamate spillover in cerebellum, neocortex and hippocampus (Okubo et al., 2010; Okubo & Iino, 2011). Multiple action potentials in a row yield sufficient spillover glutamate to activate non-synaptic NMDA and Group I mGluR receptors (which are co-expressed on NE varicosities and enhance glutamate-evoked NE release in rodent and human cortices; Luccini et al., 2007), but not lower affinity AMPA receptors (Okubo et al., 2010). Extracellular concentrations of the spillover rapidly decrease as distance from the synaptic cleft increases (Vizi et al., 2010) and the upper limit of glutamate spillover effects is estimated to be no greater than a few micrometers (Okubo & Iino, 2011).

That spillover glutamate is sufficient to activate NMDA but not AMPA receptors is another key factor. Unlike AMPA receptors, NMDA receptors require synchronized glutamate stimulation and neuron depolarization to activate (Lüscher & Malenka, 2012). Thus local glutamate spillover must co-occur with phasic depolarizing bursts of activity in LC neurons to recruit additional local NE release. Furthermore, a unique feature of NMDA receptors is that they require a coagonist, which could either be glycine or D-serine (Wolosker, 2007). Glutamate stimulates astrocytes to release these coagonists (Harsing & Matyus, 2013; Van Horn, Sild, & Ruthazer, 2013), and both glutamate and NE stimulate astrocytes to release glutamate (Parpura & Haydon, 2000). These additional glutamate interactions should further enhance NMDA receptor-mediated NE release (see Fig. 6 and Paukert et al., 2014). Together these local glutamate-NE interactions support the emergence and sustainment of hot spots in the vicinity of the most activated synapses when arousal is induced.

Consistent with the existence of glutamate-NE interactions, local NE release in the region of an activated novel representation depends on the coincident timing of the novel event and an

arousing event (Rangel & Leon, 1995). For instance, when footshock was administered to a rat while it explored a novel environment, NE levels rose substantially more and stayed elevated for longer than when footshock was administered in its holding cage (Fig. 7; McIntyre et al., 2002). The amygdala presumably activated in response to the novelty of the new environment (Weierich, Wright, Negreira, Dickerson, & Barrett, 2010), and glutamate associated with that representational network amplified the NE release initiated by the shock.

Hot spot effects have also been observed in the bed nucleus of the stria terminalis immediately after training rats on an inhibitory avoidance task (Liu, Chen, & Liang, 2009). When infused separately at low doses, glutamate and NE each had no effect. But when infused together at the same low doses, they produced marked memory enhancements. Infusing a higher dose of glutamate led to memory enhancements that were blocked by propranolol, indicating that the glutamate effect required β -adrenergic activity, which as we describe next, is another key feature of our hot spot model.

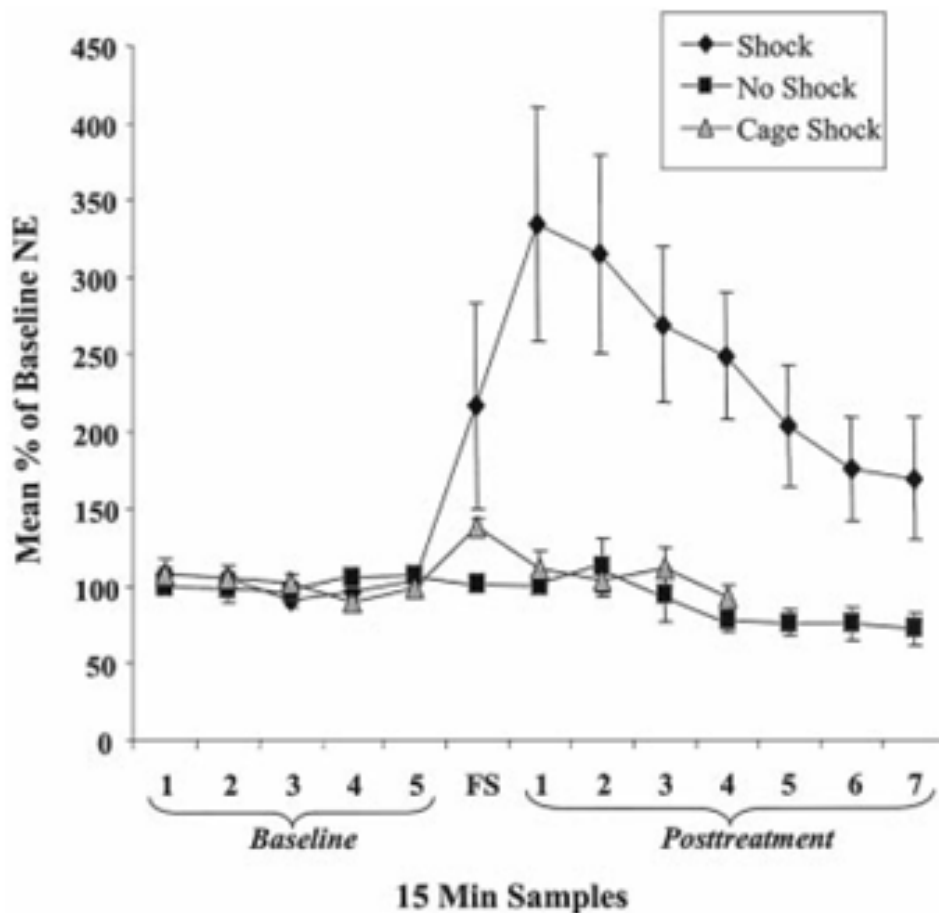


Figure 7. A rat receiving a shock in its home cage shows a brief increase in NE levels (grey triangles). A novel training environment does not increase NE on its own (black squares), but NE levels increase dramatically when shock is combined with that novel training environment (black diamonds). Figure from McIntyre et al. (2002).

2) α - and β -adrenoceptors exert different effects on neuronal excitability and require different NE concentrations to be activated. To be engaged, β -adrenoreceptors require relatively high NE concentrations, α 1-adrenergic receptors more moderate levels, and α 2-adrenergic receptors the lowest NE concentrations (Ramos & Arnsten, 2007). Thus, under arousal, α 2-adrenoceptor effects should be widespread, whereas β -adrenoreceptors should only be activated at hot spot

regions due to local glutamate-evoked NE release leading to higher NE levels. Next, we describe the importance of this distinction for adrenergic autoreceptors.

3) Adrenergic autoreceptors inhibit or amplify their own NE release. Autoreceptors at NE varicosities serve as neural gain amplifiers by taking opposing action at low and high local levels of NE. The predominant presynaptic noradrenergic autoreceptor in humans is the $\alpha 2A$ -adrenoceptor (Starke, 2001), which inhibits NE release when it detects low or moderate levels of NE (Delaney, Crane, & Sah, 2007; Gilsbach & Hein, 2008; Langer, 2008; Starke, 2001). In contrast, presynaptic β -adrenoceptors amplify NE release when activated by high levels of NE (Chang, Goshima, & Misu, 1986; Misu & Kubo, 1986; Murugaiah & O'Donnell, 1995a, 1995b; Ueda, Goshima, Kubo, & Misu, 1985). In addition, $\alpha 2A$ -adrenoceptors may lose affinity for NE when neurons are depolarized (Rinne, Birk, & Bünemann, 2013), which would remove their inhibitory influence as a region becomes highly active. However, this loss of affinity recovers at saturating levels of NE (Rinne et al., 2013), which should help prevent runaway excitation that could otherwise emerge due to the NE-glutamate feedback loop. Together with glutamate-evoked NE release (see Section 5.1.1), the opposing effects of these different auto-receptors at low and high levels of NE provide an elegant way for the LC to modulate signal gain depending on the degree of local excitation.

4) Elevated local NE at hot spots engages β -adrenoceptors on the glutamate terminals transmitting the prioritized representation. This stimulates an even greater release of glutamate, thereby amplifying the high priority excitatory signal (Ferrero et al., 2013; Gereau & Conn, 1994; Herrero & Sánchez-Prieto, 1996; Ji et al., 2008; Kobayashi et al., 2009; Mobley & Greengard, 1985). Because β -adrenoreceptors require relatively high NE concentrations to be engaged, this further biases this form of cortical auto-regulation towards the most active synapses. Through these feedback processes high priority representations are 'self-selected' to produce a stronger glutamate message and excite their connections more effectively under arousal. This stronger

glutamate message should also promote selective memory of such stimuli (see Section 6.1). In contrast, activation of lower threshold $\alpha 2$ -adrenoreceptors inhibits glutamate release (Bickler & Hansen, 1996; Egli et al., 2005), providing a mechanism for inhibiting lower priority neural activity under arousal.

5) Higher NE levels at hot spots help prolong the period of neuronal excitation by temporarily inhibiting processes that normalize neuron activity. Under normal conditions, the slow after-hyperpolarization current habituates a post-synaptic neuron's responses following prolonged depolarization (Alger & Nicoll, 1980). However, even here NE seems to benefit prioritized inputs by prolonging neuronal excitation via β -adrenoreceptors inhibiting the slow after-hyperpolarization (Madison & Nicoll, 1982; Nicoll, 1988).

In summary, different receptor subtypes enable NE to ignite hot spots in regions with high glutamate while inhibiting activity elsewhere. As we outline later on, this diversity in NE-receptor subtypes also plays an important role in shaping synaptic plasticity to favor prioritized representations under phasic arousal.

5.2. NE hot spots modulate interneurons and GABAergic transmission to increase lateral inhibition of competing representations.

Increases in glutamate and NE at hot spots should also enhance inhibitory activity that mediates competition among neurons. GABA is the most widespread inhibitory transmitter from neurons that suppress the responses of other neurons or neuronal circuits (Petroff, 2002). Strong glutamate activity in cortical circuits stimulates local GABAergic activity, which increases the inhibitory effects of highly active regions on neighboring, competing neural circuits (Xue, Atallah, & Scanziani, 2014). Increases in NE also activate inhibition directly, with intermediate concentrations engaging maximal suppression (Nai, Dong, Hayar, Linster, & Ennis, 2009).

Subtypes of interneurons respond differently to NE in ways that should further increase neural gain. While LC-NE activity activates interneurons that mediate lateral inhibition (Salgado, Garcia-Oscos, et al., 2012), it can also suppress interneurons with feedforward connections (Brown, Walling, Milway, & Harley, 2005), such that a strong signal will inhibit competing representations while enhancing activity in other neurons within its processing pathway.

5.3. NE directs metabolic resources to where they are most needed.

To optimize processing of salient events, NE also helps coordinate the delivery of the brain's energy supplies, allowing it to mobilize resources quickly when needed (e.g., Toussay, Basu, Lacoste, & Hamel, 2013). The brain's most essential energy supplies, oxygen and glucose, are delivered via the bloodstream. One key way that NE coordinates energy delivery is by increasing the spatial and temporal synchronization of blood delivery to oxygen demand within the brain. For instance, in mice, increasing NE levels decreases overall blood vessel diameter in the brain but increases the spatial and temporal selectivity of blood distribution to active task-relevant regions (Bekar, Wei, & Nedergaard, 2012).

In addition to distributing blood flow, NE also interacts with astrocytes locally to mobilize energetic resources throughout the cortex. When a particular area of the brain needs more energy, it can obtain fuel not only from glucose but also from glycogen in astrocytes (Pellerin & Magistretti, 2012). NE speeds up the process of obtaining energy from glycogen (Magistretti, Morrison, Shoemaker, Sapin, & Bloom, 1981; Sorg & Magistretti, 1991; Walls, Heimbürger, Bouman, Schousboe, & Waagepetersen, 2009). While α 1- and α 2-adrenoreceptors mediate glutamate uptake and glycogen production in astrocytes, β -adrenoreceptors stimulate the breakdown of glycogen to provide rapid energy support in highly active local regions (O'Donnell et al., 2012), further amplifying NE hot spot activity.

5.4. Summary.

At the local neuronal level, NE suppresses most activity but amplifies the strongest activity due to differential effects of NE on different adrenoceptor subtypes. The amplification of strong activity occurs via “NE hot spots,” where positive feedback loops between local NE and glutamate release increase the strength of activated representations. To sustain higher levels of activity, hot spots also recruit limited metabolic resources. At the circuit level, the increased glutamate and NE produced at hot spots recruit nearby astrocytes that supply additional energy to active neurons. On a broader scale, NE facilitates the redistribution of blood flow towards hot spots and away from areas with lower activity. Thus, by influencing multiple levels of brain function, NE selectively amplifies self-regulating processes that bias processing in favor of prioritized information.

6. Roles of the LC-NE system in memory

So far we have focused on how arousal increases the gain on prioritization processes in perception, attention, and initial memory encoding. Now we turn to memory consolidation processes. Experiencing an emotionally intense event influences the vividness and longevity of recent memory traces, enhancing or impairing them based on their priority (e.g., Fig. 4; Knight & Mather, 2009; Sakaki et al., 2014). Much research has shown that NE is involved in memory consolidation effects (for a review see McGaugh, 2013), but there has been little focus on the interplay between NE’s enhancing and impairing effects during memory consolidation.

The durability of memories depends on adjustments in the strength of communication across synapses via processes known as long-term potentiation (LTP) and long-term depression (LTD). Whether neural activity triggers LTP or LTD depends on the relative timing of spikes in pre- and post-synaptic neurons (Nabavi et al., 2014), and whether LTP and LTD are maintained depends on protein synthesis processes (Abraham & Williams, 2008). We propose that two

main NE mechanisms modulate LTP and LTD processes, leading to “winner-take-more” and “loser-take-less” outcomes in long-term memory: 1) a hot-spot modulation of the probability of LTP (higher NE levels engaging LTP) and LTD (relatively lower NE levels promoting LTD), and 2) NE-enhanced protein synthesis supporting long-term maintenance of LTP and LTD.

6.1. NE gates spike-timing-dependent LTD and LTP

LTP and LTD are often studied in brain slices in a petri dish using high frequency electric stimulation to induce LTP and repeated slow stimulation to induce LTD. But in the brain’s natural context involving constant barrages of presynaptic activity generating postsynaptic spikes, the relative timing of pre- and post-synaptic activity helps determine whether LTP or LTD occurs. Furthermore, to avoid constantly adjusting synapses up and down based on random firing patterns, neuromodulators such as NE and dopamine signal when the relationship between presynaptic and postsynaptic activity is likely to be meaningful (Pawlak, Wickens, Kirkwood, & Kerr, 2010). *In vivo* studies indicate that spike-timing-dependent LTP or LTD requires these neuromodulators (Huang et al., 2014; Johansen et al., 2014). In particular, by binding to G-coupled receptors, NE modulates kinases and phosphatases that determine whether LTP or LTD induction occur (Treviño, Huang, et al., 2012; Tully & Bolshakov, 2010).

Different adrenoreceptor subtypes appear to mediate NE’s regulation of spike-timing-dependent LTP and LTD. Spike-timing-dependent LTP is primarily initiated by β -adrenoreceptor activation, whereas α 1-adrenoreceptors promote spike-timing-dependent LTD (Salgado, Kohr, & Trevino, 2012). Critically, Salgado and colleagues showed that the LTP promoting activation of β -adrenoceptors requires ~25-fold higher concentrations of NE (8.75 micromolar) than the NE concentration that promotes α 1-adrenoreceptor-mediated spike-timing-dependent LTD (.3 micromolar) *in vitro*. This agrees with an *in vivo* estimate of a 30-fold NE increase associated with NE-LTP in dentate gyrus (Harley, Lalies, & Nutt, 1996). The required increase in NE to

support spike-timing-dependent LTP is substantially higher than increases in NE levels seen when experimenters stimulate LC and measure NE in cortex or hippocampus using microdialysis (e.g., ~twice baseline, Florin-Lechner, Druhan, Aston-Jones, & Valentino, 1996; ~.5 micromolar, Palamarchouk, Zhang, Zhou, Swiergiel, & Dunn, 2000). Thus, there is a discrepancy between the NE levels needed for spike-timing-dependent LTP to occur and the levels measured in laboratory studies. Our GANE model accounts for this difference, as it posits that LC activation interacts with prioritized representations to elicit much higher NE release in a select few local hot spots than elsewhere.

The NE hot spot model supports a range of simultaneous NE modulatory actions. At high priority hot spots, NE levels should be sufficiently high to engage β -adrenoreceptors and initiate spike-timing-dependent LTP (Salgado, Kohr, et al., 2012; Treviño, Huang, et al., 2012).

Conversely, areas with lower glutamate activity, where NE levels are by comparison modestly increased, would undergo LTD due to the engagement of relatively higher affinity α 1-adrenergic receptors (Huang et al., 2014; Salgado, Kohr, et al., 2012; Treviño, Frey, & Köhr, 2012).

Variations in NE levels in the alert brain thereby support bidirectional plasticity (Salgado, Kohr, et al., 2012; Treviño, Huang, et al., 2012).

6.2. NE increases protein synthesis processes that promote memory

consolidation: the critical role of β -adrenoreceptors

Arousal levels in the minutes and hours before or after an event also influence later memory for it. Here we review evidence that these wider time window effects of arousal depend on NE enhancing protein synthesis processes that determine the long-term durability of salient memories. Critically, such regulation of memory processes by NE appears to be mediated by β -adrenoreceptors, which we propose are selectively activated in high priority representational networks.

NE's role in gating the synthesis of plasticity-related proteins has been recognized for more than a decade (Cirelli, Pompeiano, & Tononi, 1996; Cirelli & Tononi, 2000). For instance, plasticity-related proteins promoted by an LC-NE novelty signal can enhance long-term memory consolidation of another salient but otherwise poorly consolidated event (i.e., learning that stepping off of a platform leads to a weak shock) that happens one hour later or even one hour prior to the novelty experience (Moncada & Viola, 2007; Moncada, Ballarini, Martinez, Frey, & Viola, 2011).

Blocking β -adrenoreceptors or protein synthesis prior to novelty exposure prevents novelty facilitation of LTP (Straube, Korz, Balschun, & Frey, 2003). What is particularly striking is that β -adrenoceptor activation at time 1 primes synapses to induce LTP at time 2 an hour later even when β -adrenoceptor receptors are blocked by propranolol during time 2 (Tenorio et al., 2010). However, if protein synthesis processes are blocked during time 2, the time-1 priming event does not lead to enhancement. The plasticity marker, Arc protein, is recruited by β -adrenoceptor activation in the presence of NMDA receptor activation (Bloomer, VanDongen, & VanDongen, 2008). Hot spots are characterized by high levels of glutamate release and β -adrenoceptor activation, thus emotional arousal should elevate Arc selectively in NE hot spots.

β -adrenergic activation after learning or weak LTP induction can also convert short-term LTP to more lasting protein-synthesis-dependent late-LTP (Gelinas & Nguyen, 2005; Gelinas, Tenorio, Lemon, Abel, & Nguyen, 2008). Likewise, stimulating the basolateral amygdala either before or after tetanization of the hippocampus converts early-LTP to late-LTP via a β -adrenoreceptor mechanism (Frey, Bergado-Rosado, Seidenbecher, Pape, & Frey, 2001). Activating β -adrenoreceptors also shields late-LTP from subsequent depotentiation (Gelinas & Nguyen, 2005; Katsuki, Izumi, & Zorumski, 1997).

Creating long-lasting memories depends on the protein synthesis cAMP/PKA/CREB signaling cascade (Kandel, 2012; O'Dell, Connor, Gelinas, & Nguyen, 2010). Neuronal ensembles in which the cAMP/PKA/CREB cascade has been activated, as happens with the engagement of β -adrenoceptors, have been shown to be selectively allocated to the engram representing a memory (Han et al., 2007). Furthermore, increasing excitability via different methods mimics the effects of CREB overexpression, suggesting that neurons are recruited to an engram based on their neural excitability (Frankland & Josselyn, 2015; Zhou et al., 2009). Thus, by modulating CREB and other aspects of neural excitability, NE hot spots should help determine which neurons are allocated to an engram and stabilized in long-term memory.

6.3. Summary.

Local NE concentration is the key to understanding how NE mediates arousal's dichotomous effects on memory. Previous research has shown that different NE levels regulate different forms of spike-timing-dependent plasticity by engaging distinct adrenoceptors. Whereas NE binding to moderate affinity α 1-adrenergic receptors leads to LTD and memory suppression, NE binding to lower affinity β -adrenoceptors leads to LTP and memory enhancement. We propose that local discrepancies in NE levels arise from self-regulating NE-glutamate interactions. Where NE concentrations become high enough to engage low-affinity β -adrenoceptors, a cascade of intracellular events triggers protein synthesis processes that enable long-term memory consolidation of the high priority trace. In contrast, more modest increases in NE levels at less active regions lead to LTD, ensuring less important events are forgotten. Before or after encoding, the confluence of protein synthesis and β -adrenoceptor activation selectively strengthen memory consolidation when these mechanisms are recruited close by in time.

7. Beyond local GANE: Broader noradrenergic circuitry involved in increased selectivity under arousal

Beyond local effects, NE increases biased competition processes by altering how different brain structures interact. With its widely distributed afferents, the LC-NE system influences neural processing in many brain regions when an arousing event occurs. NE release can translate local hot-spot effects to more global winner-take-more effects by modulating neuronal oscillations. Furthermore, cortical and subcortical priority signals modulate glutamate release in sensory regions and the hippocampus as mental representations are formed and sustained. As previously reviewed (see Section 5.1), glutamate is essential for NE release to selectively amplify the processing of significant information. Thus, by stimulating local glutamate release and recruiting LC firing, key brain structures can optimize synaptic conditions for arousal to ignite hot spots.

7.1. The activation of inhibitory networks by NE primes neuronal synchronization among high priority neural ensembles.

So far, we have reviewed evidence that NE hot spots amplify the effects of priority, enhancing salient features while noisy background activity is suppressed. In this section, we discuss the possibility that neuronal oscillations communicate activity in local hot spots more globally (Singer, 1993).

The first candidate is gamma synchrony (30-80 Hz). Conceptual frameworks of neural oscillations posit that gamma synchrony supports gain modulation in local networks (Fries, 2009), such that a target area can only oscillate in phase with one of two competing inputs. As a result, the synaptic input that more successfully synchronizes its activity with the target region gets amplified while the less synchronized input gets suppressed. Gamma synchrony is likely a key component of selective attention (Baluch & Itti, 2011; Fries, 2009; Fries et al., 2001).

Gamma oscillations are generated by a feedback loop between excitatory pyramidal cells and fast-spiking parvalbumin positive inhibitory interneurons (Buzsáki & Wang, 2012; Cardin et al., 2009; Carlen et al., 2012; Sohal, Zhang, Yizhar, & Deisseroth, 2009). Noradrenergic release activates these interneurons (Cox, Racca, & Lebeau, 2008; Huang, Huganir, & Kirkwood, 2013; Toussay et al., 2013) and increases gamma synchrony in these target regions (Gire & Schoppa, 2008; Haggerty, Glykos, Adams, & LeBeau, 2013; Marzo, Totah, Neves, Logothetis, & Eschenko, 2014). Emotional arousal also modulates gamma oscillations in regions that process motivational significance, such as the amygdala, sensory cortex and PFC (Headley & Weinberger, 2013). These results suggest that arousal-induced NE release selectively biases gamma oscillations in favor of the most activated representations in local neuronal ensembles.

Consistent with the hot spot model, increases in local gamma power during cognitive processing in humans are associated with increases in glutamate levels (Lally et al., 2014). Increases in local gamma power are also associated with successful memory encoding in humans (Burke et al., 2013). Likewise, in rats, fear conditioning increases gamma synchronization in sensory cortex (Headley & Pare, 2013). Increased gamma power predicts retention of tone-shock associations and enhanced representations of the tone associated with shock in the primary auditory cortex (Headley & Weinberger, 2011).

Recent research shows that β -adrenoreceptors recruit in-phase oscillations with gamma activity, while α 1-adrenoreceptors recruit out-of-phase oscillations (Haggerty et al., 2013). Given the higher threshold for activating β -adrenergic than α 1-adrenergic receptors (see Section 5.1), these results suggest that high NE levels at hot spots engage β -adrenoreceptors, recruit in-phase oscillations and increase local network connectivity for prioritized representations. Elsewhere, lower NE levels should only engage α 1-adrenoreceptors and thereby reduce local gamma power and diminish local synchronization.

In addition to modulating oscillations in local neuronal ensembles, NE also facilitates oscillatory coupling across regions. Current frameworks of neural synchrony posit that long-range/inter-regional communication between areas is modulated by oscillation in low frequency bands, such as theta (4-8 Hz), while communication within local networks is modulated by high frequencies, including gamma synchrony (Canolty & Knight, 2010; Von Stein & Sarnthein, 2000). New research further suggests that optimal network function occurs when gamma is embedded in, and phasically facilitated by, slower theta (or even delta; Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008) oscillations (Canolty & Knight, 2010; but see Burke et al., 2013). This theta-gamma coupling seems to provide a mechanism for inter-regional communication and cross-location phase coupling across regions to help translate local NE hot spots to global effects.

LC-NE system activation promotes hippocampal theta (e.g., Berridge & Foote, 1991; Walling, Brown, Milway, Earle, & Harley, 2011), and is linked to enhancement of novelty-related hippocampal theta (Kocsis, Li, & Hajos, 2007). In humans, the phase coupling of gamma with slower oscillations has been described primarily for neocortex (Canolty et al., 2006) where the LC-NE role in slower rhythms is less well studied. However, hippocampal theta entrains prefrontal cortical theta (Paz, Bauer, & Paré, 2008). Recently, selective LC-NE activation has been shown to increase neocortical theta in anesthetized animals (Vazey & Aston-Jones, 2014). The parvalbumin neurons modulated by NE participate in setting not only gamma but also theta rhythms (Varga et al., 2014; Wulff et al., 2009); thus, parvalbumin interneurons provide a mechanism for LC-NE support of phase-coupled rhythms. Indeed, lesions of NMDA receptors in the parvalbumin neurons results in decreased power of theta oscillations and reduced modulations of gamma oscillation by theta (Korotkova, Fuchs, Ponomarenko, von Engelhardt, & Monyer, 2010). NE modulation of the hyperpolarization-associated I_h current has also been proposed to support thalamocortical driving of slower neocortical oscillations (Yue & Huguenard,

2001). Thus, by modulating gamma and theta, the LC-NE system can amplify the winner-take-more effects of hot spots.

7.2. Key brain regions help evaluate priority and modulate NE hot spots

Here we review how several key brain regions help enhance GANE selectivity mechanisms under arousal. These regions help detect saliency and interact with the LC to fine-tune priority signals via their own hot-spot-like effects (e.g., amygdala) and/or other NE mechanisms (e.g., PFC and thalamus).

The amygdala plays a central role in enhancing selectivity under arousal. It helps notice and track salient information (Sander, Grafman, & Zalla, 2003) and recruits the LC when activated (e.g., Bouret, Duvel, Onat, & Sara, 2003; Fallon, Koziell, & Moore, 1978; Jones & Moore, 1977; Price & Amaral, 1981; Van Bockstaele, Colago, & Valentino, 1998). The LC in turn modulates amygdala activity via NE to further enhance the saliency signal (Sears et al., 2013). Through its strong anatomical projections to sensory cortices (Amaral, Behniea, & Kelly, 2003), the amygdala amplifies cortical processing of behaviorally relevant events (Chau & Galvez, 2012; Pessoa & Adolphs, 2010). Such modulation of other regions may be mediated by glutamate-NE interactions amplifying saliency signals within the amygdala (Fig. 7; see also Liu et al., 2009), thereby enhancing its selective modulatory influence on other regions. In addition, as reviewed previously (see Section 3.2), β -adrenoreceptors in the amygdala mediate the selective effects of arousal on memory.

The thalamus helps control the communication of sensory information across the brain (Sherman, 2005). Within the thalamus, there are dense NE fibers and high levels of NE in the pulvinar-posteriorlateral/posteriomedial complex, but very few in the lateral geniculate nucleus (Morrison & Foote, 1986; Oke, Keller, Mefford, & Adams, 1978). Through its widespread reciprocal connections with cortical and subcortical structures (Shipp, 2003), the pulvinar helps

filter inputs based on behavioral relevance (Fischer & Whitney, 2012), promotes communication across brain regions (Saalmann & Kastner, 2009; Saalmann, Pinsk, Wang, Li, & Kastner, 2012), modulates gamma oscillations (Shumikhina & Molotchnikoff, 1999), and controls the gain of sensory processing (Purushothaman, Marion, Li, & Casagrande, 2012). In addition, the pulvinar is sensitive to emotional saliency (Liddell et al., 2005; Padmala, Lim, & Pessoa, 2010; Troiani & Schultz, 2013). Thus, anatomically, NE is set up to modulate thalamic signals of priority.

Furthermore, in rats, NE increases signal-to-noise processing within the thalamus. When directly infused with NE, rat ventral posteromedial thalamus shows reduced spontaneous firing but enhanced firing in response to whisker stimulation (Hirata, Aguilar, & Castro-Alamancos, 2006). When stimulated by phasic or tonic LC activation, ventral posteromedial thalamus also showed increased firing in response to whisker stimulation (Devilbiss & Waterhouse, 2011). However, an intriguing observation was that in sensory barrel field cortex phasic stimulation of LC enhanced firing to strong whisker stimulation but slightly impaired firing to weak whisker stimulation, an outcome consistent with the NE hot spot model. However this differential response based on stimulus intensity did not occur within the ventral posteromedial thalamus, where both strong and weak sensory inputs increased firing (Devilbiss & Waterhouse, 2011). This initial finding suggests that NE influences in sensory thalamus may occur through mechanisms other than NE hot spots. Thus, further work is needed to examine NE's modulatory role in the thalamus. In any case, the thalamus plays a key role in amplifying selectivity under arousal by coordinating responses to salient stimuli across the brain. Such local representations of salient stimuli are then subject to NE modulatory influences.

The prefrontal cortex (PFC), including the OFC and ACC, has reciprocal connections with the LC (Arnsten & Goldman-Rakic, 1984; Jodo, Chiang, & Aston-Jones, 1998) and is an important regulator of LC output. PFC regions help appraise sensory information and recruit the LC based on goal-relevance (Aston-Jones & Cohen, 2005), motivational relevance (Mohanty, Gitelman,

Small, & Mesulam, 2008), reward (for the OFC; Schoenbaum & Roesch, 2005), conflict (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Sheth et al., 2012), monetary loss (Gehring & Willoughby, 2002) and pain (Rainville, Duncan, Price, Carrier, & Bushnell, 1997). The ACC is also a key site for integrating task-relevant and arousal inputs (Pessoa, 2009; Shackman et al., 2011). In humans, LC innervation of the PFC is relatively sparse, especially in anterior regions (Gaspar et al., 1989; Javoy-Agid et al., 1989), but NE modulates working memory processes in PFC (Arnsten, 2011; Wang et al., 2007).

These PFC noradrenergic influences over working memory have different mechanisms than the NE hot spot. First, in our model, β -adrenoceptors support positive feedback loops at NE-glutamate hotspots but $\alpha 2$ -adrenoceptors suppress those feedback loops (see Section 5.1). However, the facilitatory versus inhibitory roles of these adrenoceptors reverses in the context of working memory. β -adrenoceptors stimulate cAMP whereas $\alpha 2$ -adrenoceptors inhibit it (Duman & Enna, 1986; Nomura et al., 2014; Robinson & Siegelbaum, 2003). Inhibition of cAMP via stimulation of post-synaptic $\alpha 2$ -adrenoceptors increases input resistance and enhances recurrent network activity and working memory performance (Wang et al., 2007). Thus moderate levels of arousal should enhance working memory processes that maintain goal-relevant information in mind, whereas high levels of arousal should impair these processes (Arnsten, 2011; Kuhbandner & Zehetleitner, 2011). Such impairments may, in turn, disrupt initiating top-down prioritization goals after exposure to emotionally salient stimuli (Sutherland, Lee, & Mather, in preparation).

One interesting question is what might occur when top-down and bottom-up priority conflict. The insula plays a key role in this aspect and integrates salience signals from internal and external stimuli (Craig, 2009; Uddin, 2015). The insula is involved in various types of saliency processing, including error detection (Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010), interoception (Craig, 2009), oddball detection (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012),

aversive memory (Miranda & McGaugh, 2004), and detection of events that require cognitive resources (Cai et al., 2015). Although not much is known about LC-insula interactions, the LC and other NE brainstem sites project to the insula (at least in rats; Robertson, Plummer, de Marchena, & Jensen, 2013). Neuroimaging studies also suggest that elevated LC-NE activity is associated with encoding-related activity in the insula to aversive stimuli (Clewett, Schoeke, & Mather, 2014; Rasch, Spalek, Buholzer, Luechinger, Boesiger, Papassotiropoulos, & Quervain, 2009). Consistent with GANE, motivated (higher priority) versus passive viewing of emotional faces enhances functional connectivity within a face-processing network, including the insula and LC (Skelly & Decety, 2012; but see Astafiev, Snyder, Shulman, & Corbetta, 2010 for caution when interpreting results from LC fMRI).

7.3. NE amplifies activity in behaviorally relevant functional brain networks

Along with the dorsal ACC, the insula is a key node in a broader “salience network” (Eckert et al., 2009; Hermans et al., 2011) that helps integrate different sources of saliency (Seeley et al., 2007), guide adaptive behavior (Bressler & Menon, 2010; Cocchi, Zalesky, Fornito, & Mattingley, 2013), and regulate shifts from rest to task-oriented behavior (Sidlauskaite et al., 2014). Based on these findings, recent models of the salience network propose that it mediates competitive interactions between antagonistic attention networks that prioritize internal versus external stimuli (Bressler & Menon, 2010; Menon & Uddin, 2010). Current data suggest that the LC-NE system modulates salience network activity. For instance, β -adrenoreceptor blockade during stress reduces salience network activity (Hermans et al., 2011), and salience network activity is associated with pupil and autonomic responses to errors (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005) and overall arousal (Sadaghiani & D'Esposito, 2014). In neuroimaging studies, the LC co-activates with the dorsal anterior cingulate during the detection of novel stimuli (Krebs, Fias, Achten, & Boehler, 2013) and during task switching (von der

Gablenz, Tempelmann, Münte, & Heldmann, 2015), a proposed function of the salience network.

Anatomically, activating the LC-NE system is well positioned to modulate activity based on priority, as some of the most dense NE innervation is to fronto-parietal regions (Gaspar et al., 1989; Javoy-Agid et al., 1989; Morrison & Foote, 1986) that coordinate attention to salient stimuli via priority maps (Ptak, 2012). Indeed, phasic LC responses, as indexed by pupil dilation, correlate with activity in a dorsal fronto-parietal network during focused attention (Alnæs et al., 2014). However, more generally, according to GANE, activating the LC-NE system should amplify activity in whichever functional network is transmitting high priority information.

Consistent with a role of NE in mediating this process, while subjects rest, pupil dilation precedes the moment of maximal antagonism between competing cortical networks, with motor network activity being suppressed and task-negative network activity being enhanced (Yellin, Berkovich-Ohana, & Malach, 2015). In addition, NE preferentially enhances ventral fronto-parietal attention network activity during the detection of salient events that trigger re-orienting (Corbetta, Patel, & Shulman, 2008; Strange & Dolan, 2007). Thus, NE's influence on gain modulation also manifests at the whole-brain level.

7.4. Summary.

Arousal's dual effects on cognition pervade multi-level brain systems to amplify the priority of important information. By modulating theta and gamma oscillations, NE preferentially synchronizes activity between high-glutamate regions, leading to "winner-take-more" effects in perception and memory. Like some earlier emotion-cognition theories (e.g., Pessoa & Adolphs, 2010), GANE favors the perspective that the amygdala coordinates information transfer within broader networks that influence salience processing and is not the only route by which NE enhances processing of prioritized stimuli. Brain regions that evaluate saliency modulate LC

activity either via direct afferent inputs or indirectly via broader networks. Without contextual signals from these central structures and the periphery, the LC would be blind to salient events that demand attention (Sara & Bouret, 2012). In turn, the resulting increase in NE release activates these modulatory structures to further bias neural processing in favor of high priority stimuli. On a larger scale, NE modulates activity in a salience network that mediates competitive interactions between fronto-parietal attention networks supporting higher-level representations of priority. Thus, according to GANE, reciprocal interactions between the LC and hierarchical brain networks help strengthen and reinforce priority-biasing signals under phasic arousal (see Fig. 8).

Glutamate Amplifies Norepinephrine Effects (GANE) Model

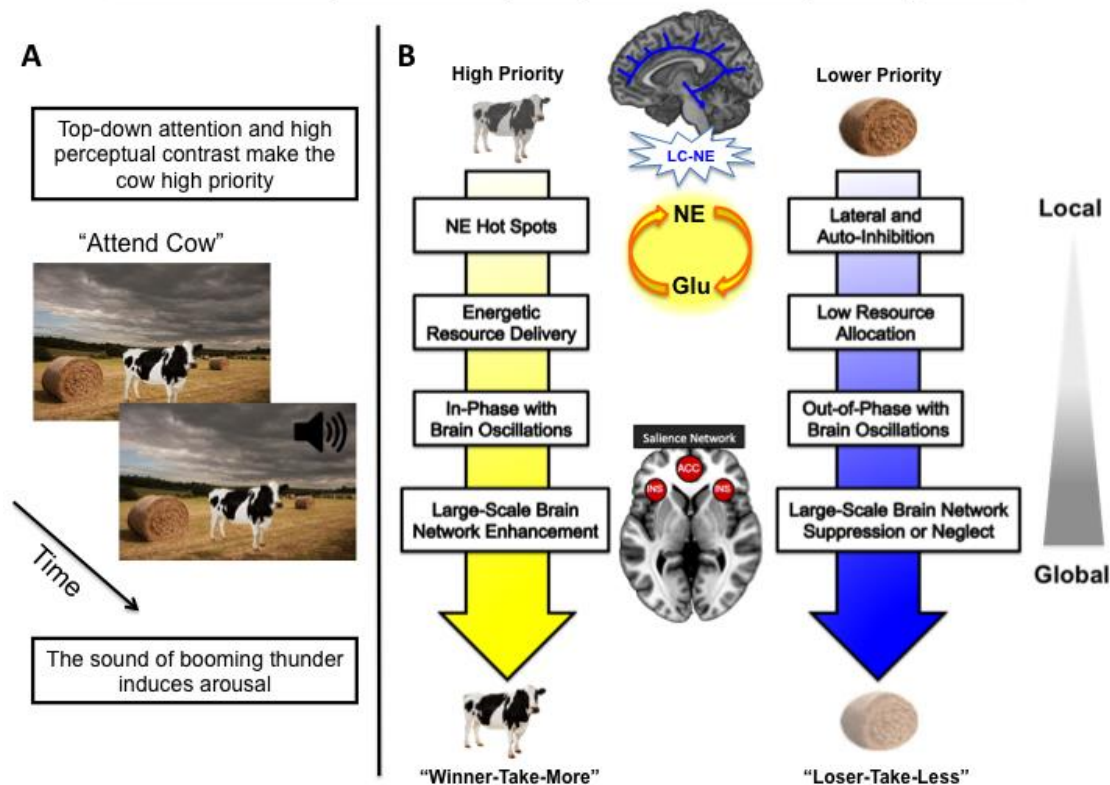


Figure 8. Summary of the GANE model. (A) An example of how arousal biases perception and memory to favor prioritized information. High perceptual contrast (bottom-up) and top-down attention prioritize processing the cow stimulus in the brain over a less salient hay bale. The

sound of booming thunder induces arousal and triggers phasic NE release. (B) Salience-evaluating structures, such as the amygdala and PFC, recruit LC firing to enable NE to modulate ongoing processing at multiple levels of brain function. In the high priority processing pathway, NE interacts with high local glutamate to create “hot spots” that increase the “cow” representational activity even further. These local hot spots recruit energetic resources, synchronize oscillations, lead to enhanced activity in high priority large-scale networks, and increase synaptic plasticity. Local glutamate-NE effects occur in parallel with more broad-scale suppression, as NE recruits lateral and auto-inhibitory processes that suppress weaker glutamate signals in lower priority processing pathways. Together these noradrenergic mechanisms lead to “winner-take-more” and “loser-take-less” outcomes in perception and memory under arousal, such that the cow is even more likely to be remembered, whereas the hay bale is even more likely to be forgotten.

8. Existing models of LC modulation of cognition

In the next section, we discuss how GANE relates to existing theories of LC neuromodulation of cognition that we have not already discussed.

8.1. Adaptive Gain Theory

The **Adaptive Gain Theory** (Aston-Jones & Cohen, 2005) posits that two different modes of LC activity (phasic vs. tonic) adaptively adjust the gain of cortical information processing to optimize behavioral performance. Phasic LC activity serves as a temporal attentional filter to selectively process task-relevant stimuli and filter out task-irrelevant stimuli, whereas tonic LC activity regulates overall arousal level in the brain. Phasic LC responses to target detection are constrained by background LC activity and occur most frequently during moderate levels of tonic activity (Usher, Cohen, Servan-Schreiber, Rajkowski, & Aston-Jones, 1999). This theory provides similar predictions to GANE in terms of the role of the phasic LC mode: phasic LC

activity should increase the gain of task-relevant inputs over noisy or task-irrelevant activity. Our model provides a neuromechanism for these effects by proposing that low-to-moderate NE levels create ideal conditions to ignite and sustain local NE hot spots via greater phasic LC responses. In support of this notion, a recent fMRI study used baseline pupil dilation before trials of a reward-learning task as a measure of tonic LC-NE activity (Eldar, Cohen, & Niv, 2013). Both low baseline pupil diameter before the trial and high pupil dilation response during the trial were associated with stronger brain activation in response to task-relevant but not task-irrelevant stimuli.

8.2. Network Reset Theory

The LC-NE system activates to various salient stimuli, including novel, uncertain, or emotionally salient stimuli (Sara, 2009; Yu & Dayan, 2005). The **Network Reset Theory** proposes that, when these stimuli are detected, the LC issues a phasic “reset” signal that reorganizes neural networks to facilitate behavioral and cognitive shifts accordingly (Bouret & Sara, 2005; Sara & Bouret, 2012). This theory explains why emotionally salient stimuli and the sudden onset of goal-relevant or perceptually salient stimuli are preferentially perceived and remembered: these events activate LC, which then reconfigures functional brain networks to process new sources of priority while impairing ongoing processing of other stimuli. This model, however, does not offer a clear explanation about why phasic arousal induced when encountering emotional stimuli can *enhance* processing of preceding stimuli when they have high priority.

To explain both the facilitative and impairing effects of emotional arousal on preceding stimuli, GANE posits that the incidental release of NE by something emotional can instead maintain - or even enhance - ongoing functional network connectivity when those networks are highly activated. Stimulating the LC can inhibit feedforward inhibition by interneurons, thereby increasing the throughput of coincident sensory (glutamatergic) inputs (Brown et al., 2005).

While this “loosening” of neurotransmission enables network flexibility and the building of a new representations, GANE’s prediction that strong glutamatergic signals transmitting a prioritized representation will benefit from sudden LC activation explains how the “reset” signal triggered by phasic LC activity can still enhance processing of preceding high priority stimuli.

8.3. Summary

GANE both complements and extends previous models of how cognition is influenced by the LC-NE system. According to Adaptive Gain Theory, high phasic LC activity promotes exploitation of the current focus of attention over exploration of other options. In contrast, the Network Reset Theory proposes that phasic LC activity promotes a global reset of attention. GANE reconciles these two theories by highlighting the role of priority. According to GANE, if the current focus of attention has sufficient priority to yield high glutamate release in synapses transmitting those stimuli, then a phasic increase in LC activity should enhance processing of those representations. Otherwise, increases in LC activity should shift attention and neural resource allocation towards new sources of priority.

GANE extends current models of LC function by positing that, under arousal, local glutamate-NE interactions will amplify activity of high priority representations regardless of how those representations initially became highly active. Thus, while GANE provides neural mechanisms that account for arousal increasing biased competition outcomes, it can also accommodate other models or modes of information prioritization (Friston, 2010; Keitel, Andersen, Quigley, & Müller, 2013; Reynolds & Heeger, 2009; Wieser, McTeague, & Keil, 2011).

9. Potential boundary conditions and questions for future research

In the current paper, we have argued that arousal leads to winner-take-more and loser-take-less effects in perception and memory via local and global noradrenergic mechanisms in the brain.

Yet, while GANE explains many findings observed in the emotion-cognition literature, there are a number of important questions for future research.

First, arousal may not increase selectivity as effectively among older adults because of age-related changes in the LC-NE system, including loss of LC neurons (Manaye, McIntire, Mann, & German, 1995; Sladek Jr & Sladek, 1978; Vijayashankar & Brody, 1979). Recent autopsy evidence indicates that lower LC neuron density is related to the rate of cognitive decline prior to death, even after controlling for decline in other aminergic nuclei (e.g., dorsal raphe, ventral tegmental area; Wilson et al., 2013). β - and α 2-adrenoreceptors may also be affected in aging. In a human postmortem sample, there was no correlation with age in overall β -adrenoreceptors but an increase in the β 2/ β 1 ratio (Kalaria et al., 1989). Decreases in α 2-adrenoreceptor activity may contribute to age-related cognitive declines, as agonists that engage α 2A-adrenoreceptors can improve age-related deficits in working memory (Arnsten & Cai, 1993; Arnsten & Goldman-Rakic, 1985; Ramos, Stark, Verduzco, van Dyck, & Arnsten, 2006). This α 2A-induced recovery of working memory may be mediated by improvements in the ability to maintain focused attention (Decamp, Clark, & Schneider, 2011). Aging also affects how effectively glutamate triggers additional NE release (Gonzales et al., 1991; Pittaluga, Fedele, Risiglione, & Raiteri, 1993), which would disrupt the emergence and/or efficacy of NE hot spots in older adults.

Another question is the role of sleep, which plays a crucial role in selectively consolidating salient memory traces (Diekelmann & Born, 2010), including emotional stimuli (Hu, Stylos-Allan, & Walker, 2006; Payne, Stickgold, Swanberg, & Kensinger, 2008; Payne, Chambers, & Kensinger, 2012) and top-down prioritized information (Rauchs et al., 2011; Saletin, Goldstein, & Walker, 2011). Emerging research suggests that the LC-NE system may enhance memory consolidation during slow wave sleep (NREM), a period when high priority neural ensembles reactivate (for a review, see Sara, 2010; Dang-Vu et al., 2008; Eschenko, Magri, Panzeri, & Sara, 2012). For instance, there is a learning-dependent increase in LC activity during slow

wave sleep (SWS ; Eschenko & Sara, 2008) and depleting NE prior to encoding reduces SWS that night (Cirelli, Huber, Gopalakrishnan, Southard, & Tononi, 2005). Pharmacologically enhancing LC-NE system activity during SWS improves recognition of odors learned within the previous three hours, whereas blocking LC-NE activity impairs odor recognition (Gais, Rasch, Dahmen, Sara, & Born, 2011). Blocking NE during sleep also leads to greater memory impairment for emotional than for neutral stimuli (Groch et al., 2011). The timing of transient LC activity coincides with the slow-wave grouping of hippocampal sharp-wave ripples complexes and sleep spindles that promote NMDA-mediated cellular plasticity (Diekelmann & Born, 2010; Rosanova & Ulrich, 2005). NE may interact with these processes, given evidence that pharmacologically activating β -adrenoreceptors facilitates the emergence of sharp-waves and the induction of LTP (Ul Haq et al., 2012). Together these findings raise the intriguing possibility that the precise timing of NE release interacts with the reactivation of high-priority memory networks to facilitate GANE effects during SWS.

In this paper, we focused on perception, encoding and consolidation processes, but another important question for future research is how NE modulates memory retrieval (e.g., Sterpenich et al., 2006). For instance, when encountering a new experience, our memory system needs to decide whether this novel information will be stored as a distinct memory (i.e., requiring pattern separation) or used to reactivate existing memories (i.e., requiring pattern completion; Bakker, Kirwan, Miller, & Stark, 2008). Previous research showed that arousal facilitated pattern separation (Segal, Stark, Kattan, Stark, & Yassa, 2012) and that NE facilitated retrieval or pattern completion (Devauges & Sara, 1991). But it has been unclear how NE/arousal modulates competition between these two hippocampal processing modes. GANE might also affect the stability of a salient memory *after* it is retrieved, or re-consolidated, since this process involves β -adrenoreceptor and NMDA receptor activation (Lee, Milton, & Everitt, 2006; Przybyslawski, Roullet, & Sara, 1999).

Another open question is the timing of these effects. Behavioral data indicate that presenting an emotionally salient item influences memory of items appearing in the past few seconds (e.g., Sakaki et al., 2014) and memory of items appearing in the next few seconds, as well (e.g., Sutherland & Mather, 2012). It is plausible that the phasic release of NE would have effects on this time scale, but research examining NE-glutamate interactions is needed to address this question.

On the tonic side of the equation, events that induce stress activate both the LC-NE system and the hypothalamic pituitary adrenal (HPA) axis (Pacak & Palkovits, 2001; Sved, Cano, Passerin, & Rabin, 2002) and these two systems interact in many ways, especially via the actions of corticotropin releasing factor (CRF). Released by the hypothalamus under stress, CRF helps to initiate the HPA axis response while also targeting the LC (Carrasco & Van de Kar, 2003; Valentino & Van Bockstaele, 2001; Van Bockstaele, Bajic, Proudfit, & Valentino, 2001). CRF influences both tonic LC activity and sensory-evoked phasic discharge - either enhancing or impairing sensory-evoked phasic responses depending on waking state and CRF levels administered (Bangasser & Valentino, 2012; Devilbiss, Waterhouse, Berridge, & Valentino, 2012; Zitnik, Clark, & Waterhouse, 2014). One possibility is that by modulating tonic levels of LC activity, stress also enhances or constrains the impact of phasic arousal responses (see Section 8.1).

Human genetic studies suggest that different NE polymorphisms moderate the strength of arousal's influence on memory and perceptual processing. To date, much of this research has focused on the ADRA2B-deletion variant in which there is reduced NE inhibitory signaling. Human ADRA2B-deletion carriers show greater activity in the amygdala and insula during the viewing or encoding of emotional versus neutral images (Cousijn et al., 2010; Rasch, Spalek, Buholzer, Luechinger, Boesiger, Papassotiropoulos, & de Quervain, 2009). Such patterns of NE-related activity are believed to underlie the larger advantage of emotionally salient over

neutral stimuli in memory (de Quervain et al., 2007) and perception (Todd, Palombo, Levine, & Anderson, 2011; Todd et al., 2013) observed in these individuals.

However, it is unclear how these genetic effects relate to the NE hot spot mechanisms outlined in GANE. Whereas $\alpha 2A$ -adrenoreceptors are found throughout much of the brain and have been clearly identified as autoreceptors regulating NE release, the $\alpha 2B$ receptors associated with this genetic polymorphism have a different profile (Brede, Philipp, Knaus, Muthig, & Hein, 2004). They are most dense in striatum, globus pallidus and thalamus (Saunders & Limbird, 1999; De Vos, Vauquelin, Keyser, Backer, & Liefde, 1992) and are essential for regulating the fetal blood supply (Brede et al., 2004). Thus, although it is possible that these genetic effects alter the feedback cycle in NE hot spots, the genetic differences could also be mediated by different developmental pathways, thalamic modulation of emotional input, or some other factor.

Related to this point about the differential brain localization of $\alpha 2B$ -adrenoreceptors is the more general question of how regional variation in receptor density (e.g., Zilles & Amunts, 2009) will modulate hot spot effects. Modeling and direct comparisons of NE-glutamate interactions across regions could help address this question.

In addition, while we have focused on how the LC-NE system influences cognition, other neuromodulators such as serotonin, dopamine and acetylcholine share many mechanisms of action with NE (Hurley, Devilbiss, & Waterhouse, 2004) and interact with NE to regulate attention, memory, and arousal (Arnsten, 2011; Briand, Gritton, Howe, Young, & Sarter, 2007; Sara, 2009). Such interactions are likely to modulate the NE-glutamate interactions highlighted here (some examples already described in Section 5.1 are interactions with orexin, histamine, glycine and serine). These interactions may allow for more nuanced effects and some redundancy within the arousal system. However, given NE's core role in arousal and broad innervation of much of the brain, including source nuclei of other neuromodulators (e.g., ventral

tegmental area and basal forebrain; Jones, 2004; Sara, 2009), we expect that it plays the lead role in modulating cognitive selectivity as arousal levels fluctuate.

10. Conclusion

Selection is at the core of what allows our cognitive systems to function effectively, allowing us to process the constant influx of information and retrieve the experiences most relevant for adaptive behavior and maintenance of wellbeing. The ability to focus on salient information is especially important during situations that induce arousal, such as during exposure to threatening or exciting sounds or objects, or the pressure to perform a challenging task. For over 50 years, there has been robust behavioral evidence that arousal often simultaneously enhances and impairs processing of different types of neutral information (Easterbrook, 1959). Yet brain-based accounts of how arousal influences cognition failed to address how such dual effects could arise.

Our GANE model fills this critical gap. In this framework, we propose that increases in NE levels under arousal enhance the selectivity of information processing. GANE builds on the previous arousal-biased competition (ABC) model to provide neural mechanisms of how NE leads to winner-take-more and loser-take-less effects in perception, attention and memory. However, unlike ABC, GANE does not require competition to be a fundamental mechanism. Instead, GANE selectively amplifies the activity of whatever priority mechanisms are operating.

Under phasic arousal, local glutamate signals corresponding to a highly activated percept interact with NE to create a hot spot of even higher levels of activity, while lower priority representations are either neglected or further suppressed. These self-regulating hot spots are further aided by NE's recruitment of brain structures and large-scale functional networks that determine which stimuli deserve attention. NE directs blood flow and energetic resources to brain regions transmitting prioritized information. It supports selective memory consolidation via

initiation of LTP and LTD. Through all of these processes, NE increases the gain of prioritized information in the brain, such that things that matter stand out even more and are remembered even better, while the mundane or irrelevant recede even more into the background and are ignored or forgotten.

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Table 1. Brain-based emotion-cognition theories

	Description	Inconsistent/unexplained findings
<i>Models that focus on enhancement for emotionally salient stimuli</i>		
Multiple attention gain control model (Pourtois, 2013)	The amygdala and other modulatory regions amplify emotional salience signal in the sensory pathway <i>in parallel with</i> bottom-up and top-down systems.	Emotional arousal can enhance perception of not only emotional information but also non-emotional information.
Multiple waves model (Pessoa & Adolphs, 2010)	The amygdala and other modulatory regions <i>coordinate</i> activity in attention systems to enhance perception.	Emotional arousal does not always enhance perception.
Amygdala modulation model of memory (McGaugh, 2004)	The amygdala enhances processing in other memory-related regions to enhance memory for emotional events via the noradrenergic mechanisms.	NE-amygdala interactions enhance memory not only for emotional stimuli but also for non-emotional stimuli.
<i>Models that capture selective effects of emotion</i>		
Biased Attention via Norepinephrine model (BANE; Markovic et al., 2014)	The anterior affective system detects emotional saliency and recruits the LC-NE system to bias attention and memory in favor of emotionally salient stimuli.	Emotional information sometimes enhances perception and memory for nearby neutral information.
Dual competition model (Pessoa, 2009)	Emotional stimuli compete for resources with other stimuli, leading fewer resources available for non-emotional stimuli.	Emotional information sometimes enhances perception and memory for nearby neutral information.
Ruthless competition model (Diamond, 2005)	Encoding new emotional information suppresses recently potentiated synapses, resulting in enhanced memory for emotional information at the cost of preceding events.	Emotional arousal enhances memory for what has happened earlier if the preceding event is emotional.
Emotional-tagging hypothesis (Richter-Levin & Akirab, 2003)	Memories for emotional events are tagged, which allows for subsequent arousal to selectively enhance memory for preceding emotional events.	Emotional arousal can produce retrograde enhancement even when preceding information is non-emotional.